THE KIDNEY

An Outline of Normal and Abnormal Structure and Function

By

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and

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PREFACE TO THE THIRD EDITION

SINCE the second edition, Pitts' *Physiology of the Kidney and Body Fluids* has appeared, together with several large textbooks dealing mainly with renal disease Among those written in English there have been Black's *Renal Disease*, Strauss and Welt's *Diseases of the Kidney* and Heptinstall's account of the *Pathology of the Kidney* In French there have been Hamburger, Richet, Crosnier, Antoine, Ducrot, Funck Brentano, Méry and de Montera's exhaustive two volume work *Néphrologie*, and Royer, Mathieu and Habib's excellent book on renal diseases in children These have made my task easier in that they have permitted me to concentrate on the important and interesting aspects of renal function and disease In this edition, therefore, three chapters have been removed Several others have either been completely rewritten or drastically revised including Renal Function, Selective Disturbances of Tubular Function, Unilateral Renal Disease and Hypertension, the Treatment of Terminal Renal Failure, Renal Infections and the relation between uric acid and the kidney

I am again grateful to Miss J Foxworthy, Miss P Leicester and Mr B Armitage for their continued help

H E de W

London

PREFACE TO THE FIRST EDITION

THE purpose of this book is to present an outline of renal structure and function of the normal and diseased kidney It is intended for students, but I hope it may also be useful to others who wish to know more about the subject

At the beginning there is a short description of normal structure and function, and the methods used to obtain information about each are discussed. There then follows a description of the four main syndromes which occur in renal disease, i e the nephrotic syndrome, acute renal failure, chronic renal failure, and the acute nephritic syndrome, there is also a section on the relationship between disturbances of renal function and electrolyte disorders The second half of the book consists principally of an account of renal diseases, including the renal manifestations of some generalised diseases These are discussed in terms of the patterns of functional disturbance which have been described in the previous sections. Unless, therefore, the reader is already familiar with the subject it is best that he should start at the beginning or at least read the sections on the four syndromes and electrolyte disturbances before those on specific renal disorders.

For the sake of clarity, I have to confess that I have over-simplified many controversial subjects and in some instances given only one explanation where several exist. I have not attempted a comprehensive classification of renal disease, for in the present state of knowledge I doubt whether it is possible to arrive at a classification whose subdivisions are at the same time mutually exclusive and collectively exhaustive. Renal tuberculosis, hydronephrosis, calculi, renal tumours and certain other predominantly surgical conditions have been excluded.

I am indebted to the many workers and writers who have preceded me and I should like particularly to mention the following sources of information ; Homer Smith's textbooks of renal physiology ; A. C. Allen's histological textbook, " The Kidney ". A. M. Fishberg's " Hypertension and Nephritis " ; T. Addis' " Glomerular Nephritis " ; R. W. Lippman's " Urine and the Urinary Sediment " and G. W. Pickering's " High Blood Pressure ". As a guide to more detailed reading there is a list of references at the end of each section.

I am grateful to Drs. B. E. Miles, R. R. McSwiney, D. M. Nutbourne, F. del Greco, R. D. Grainger, A. Herxheimer, Mr. K. E. D. Shuttleworth, Mr. R. D. de Vere, and Miss I. Maureen Young for their generous help with the manuscript and for giving me the benefit of their advice. I am also indebted to Drs. A C. Dornhorst and M. S. R. Hutt, and Mr. M. Williams for their most helpful comments and for scrutinising the proofs. I wish to thank Miss J. Dewe and Miss P. Leicester for the patience and care with which they drew Figs. 1, 2, 4, 5, 6, 71 to 74, and Figs. 51, 53 to 60, and 68, respectively ; and Mr. A. L. Wooding and Mr. B. Kentish for the photographs of the figures. I am also glad to acknowledge the help of Mr. F. A. Tubbs, Miss M. E. Warner, Miss M. Matthews and Miss M. Studart in checking the references, and that of Miss J. Buchanan for her investigations on my behalf.

I am indebted to Drs. W. J. Griffiths, R. R. McSwiney, J. R. Colley and W. W. Holland for Figs. 9 and 38.

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1

THE STRUCTURE OF THE KIDNEY

A KIDNEY contains about 1,000 000 nephrons Each nephron is a thin tube approximately 20–50 μ wide and 50 mm long with one end closed and the other opening into a collecting duct The total length of the tubules in the two kidneys is about 70 miles, or more than the distance between London and Brighton The blind upper end of each nephron lies in the cortex, invaginated and expanded by a cluster of capillaries (the glomerulus) next to the glomerulus the tube is coiled into a compact mass (the proximal tubule), it then plunges straight towards the hilum of the kidney, sometimes reaching into the medulla for a variable distance, it turns back in a tight hairpin bend (the loop of Henle) and once again lies in a coil (the distal tubule) next to its own glomerulus Finally it straightens out and together with several other distal tubules joins a collecting duct, either *in or near* the medulla Several collecting ducts join together and empty their contents into larger tubes called the papillary ducts which open *directly on the surface of the papillæ (Fig 1 1)*

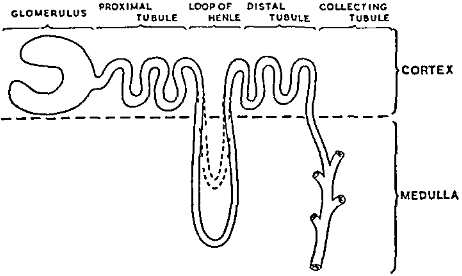

FIG 1 1 Schema of the structure of the nephron and its distribution between the cortex and medulla

Most of the proximal and distal tubules lie in the cortex, while the loops of Henle and the collecting ducts form the bulk of the medulla.

Glomerular Structure

The glomerulus is composed of 4–6 capillary loops which spring from the afferent arteriole and end in the efferent arteriole; they lie within a space whose peripheral wall is known as the glomerular capsule (or Bowman's capsule). This cluster of capillaries shares a central stalk of mesangial cells (Fig. 1.2), the cytoplasm of which forms one continuous cytoplasm while the outer part of the stalk is hollowed out to form the lumens of the capillary loop. The total surface area of the glomerular capillaries of two human adult kidneys is about 1·5 square metres. The wall of each capillary loop consists of a sandwich of epithelial cell cytoplasm, basement membrane and endothelial cell cytoplasm. The endothelial cells lie with their " backs " to the mesangial cells from which they can only be distinguished by electron microscopy. The mesangial cell is of mesenchymal origin. In normal circumstances it gives rise to the endothelial cells. In pathological circumstances, however, it may lay down connective tissue, e.g. collections of basement membrane, collagen fibres or large masses of fibrocytic cells.

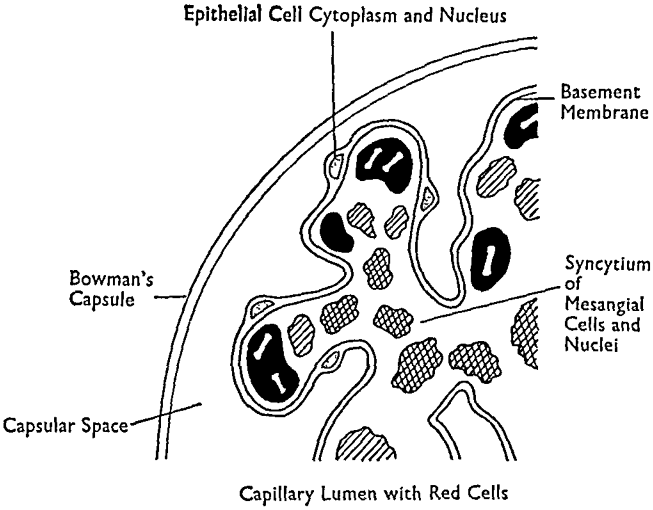
Epithelial Cell Cytoplasm and Nucleus
Basement Membrane
Syncytium of Mesangial Cells and Nuclei
Bowman's Capsule
Capsular Space
Capillary Lumen with Red Cells

FIG. 1.2. Glomerulus. High magnification schema of a portion of the glomerulus to show that the lumens of the glomerular capillaries are situated at the periphery of a syncytium of mesangial cells. The inner surface of the capillary is formed from a prolongation of endothelial cell cytoplasm while the peripheral outer surface is covered by epithelial cell cytoplasm; basement membrane lies between.

Electron microscopy has demonstrated that the cytoplasm of the epithelial cells is divided peripherally into numerous thin extensions, and that these lie in contact with the basement membrane covering the capillary loops (Fig 1 3) The surface of the loops is therefore covered by a vast number of interdigitating processes Between these processes there is a thin (70 Å) *membrane of epithelial cytoplasm* Similarly, the cytoplasm of the endothelial cells, where it forms the inner surface of the capillary loop has round punched out areas approximately 600 Å wide where the thickness of the cytoplasm is also about 70 Å The *basement membrane has a thickness of 800 Å Glomerular filtrate has* therefore to pass not only through the basement membrane but also through thin layers of both epithelial and endothelial cytoplasm The basement membrane has a homogeneous marzipan like structure The cytoplasm of the mesangial cell syncitium consists of fine fibrils embedded in a more homogeneous ground substance similar to but not identical with that of basement membrane

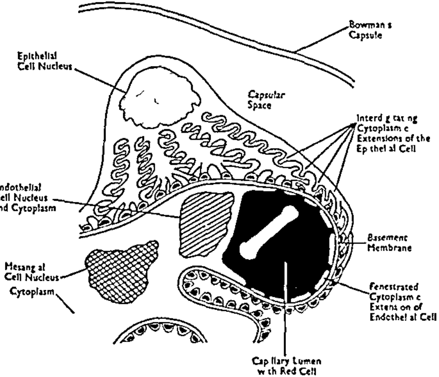
Bowman's Capsule
Epithelial Cell Nucleus
Capsular Space
Interdigitating Cytoplasmic Extensions of the Epithelial Cell
Endothelial Cell Nucleus and Cytoplasm
Basement Membrane
Mesangial Cell Nucleus
Cytoplasm
Fenestrated Cytoplasmic Extension of Endothelial Cell
Capillary Lumen with Red Cell

FIG 1 3 Glomerulus Schema of the electron microscopy appearances of a cross-section of a single glomerular capillary

Structure of the Tubule

The outer surface of the whole nephron is covered by a continuous layer of basement membrane. The proximal tubule is composed of irregularly cuboidal cells with coarse granular cytoplasm and ragged inner margins (the brush border). The cells of the descending thin limb of the loops of Henle are extremely thin and flat and have clear cytoplasm, whereas about two-thirds of the ascending limb is composed of cuboidal cells and is known as the thick part of the ascending limb. The length of the loops varies greatly; those that originate from glomeruli near the cortico-medullary junction are the longest and penetrate deeply into the medulla. The cells of the distal tubules are cuboidal but they are smaller than those in the proximal tubules; they have clear cytoplasm and sharp margins.

With the electron microscope the brush border of the proximal

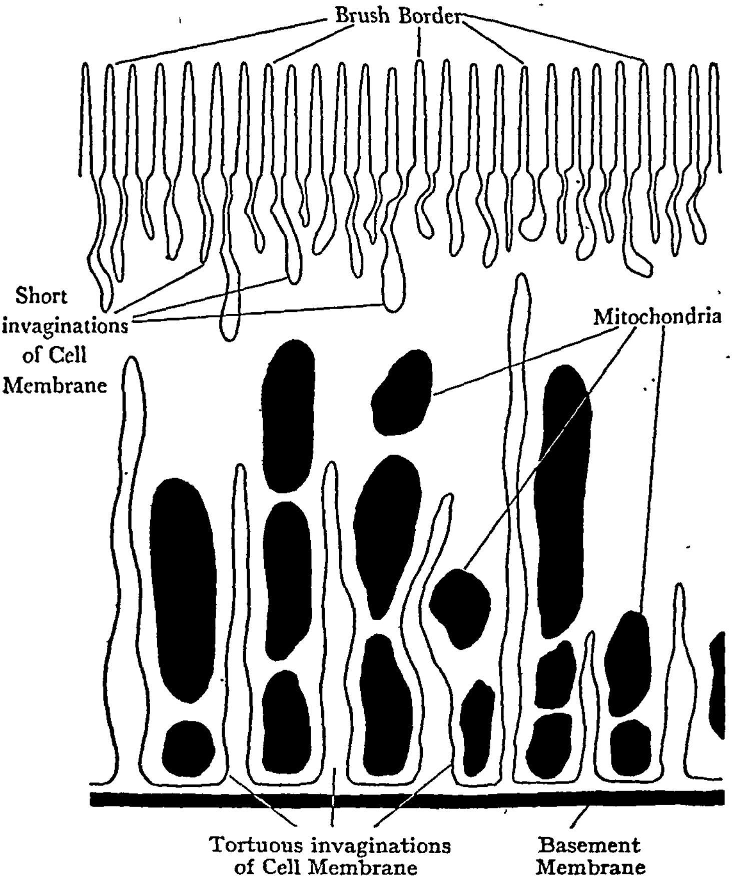
Brush Border
Short invaginations of Cell Membrane
Mitochondria
Tortuous invaginations of Cell Membrane
Basement Membrane

FIG. 1.4. Tubule. Schema of the electron microscopy appearances of a proximal tubule cell; the nucleus has been omitted.

tubule cells is seen to consist of multiple projections of cell cytoplasm about 1μ long covered by surface membrane Between these projections invaginations of the surface membrane penetrate into the cell cytoplasm and extend towards the mitochondria These projections and invaginations *increase enormously the area of contact between the tubular* fluid and the contents of the cells The membrane of the surface which lies next to the peritubular venous capillaries is also invaginated into a number of pockets which lie between the basal mitochondria (Fig 1 4) The cells of the distal tubules can readily be distinguished from those found in the proximal or collecting tubule but it has been shown that cells with the appearances of those found in the distal tubule extend down into the collecting tubules This is in keeping with the fact that those functions which are characteristic of the distal tubule also take place in the collecting tubule (p 41)

Cortico medullary Junction

At the junction of the cortex with the medulla there is a thick wide meshed fibrous net to which the renal pelvis is attached and through which the medulla and pyramids project The vessels and lymphatic channels lie outside the lumen of the pelvis and have to travel up to the cortico-medullary junction before they can enter into *the renal parenchyma*

Renal Vasculature

About 20 per cent of kidneys have multiple renal arteries i e they have an artery arising from the aorta or the iliac artery in addition to the main renal artery The renal artery divides into five segmental arteries (Fig 1 5) It is important to note that apart from the two

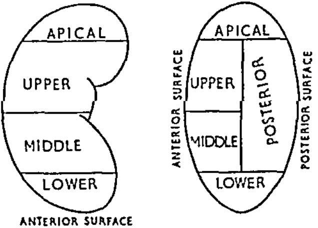

Fig 1 5 Segmental distribution of renal arterial supply poles, separate arteries supply the anterior and posterior surface of the kidney. In an ordinary antero-posterior view therefore angiography will reveal abnormalities of the arterial supply of the two poles, but isolated lesions of the arterial supply to the rest of the kidney may be obscured by overlying kidney substance to which the arterial supply is normal. At the cortico-medullary junction, the branches of the renal artery divide and lie in the long axis of the kidney. These branches are known as the arcuate arteries and contrary to original descriptions, they are only linked together by capillary connections (Fig. 1.6). The interlobular arteries branch off at right angles to these arcades, and

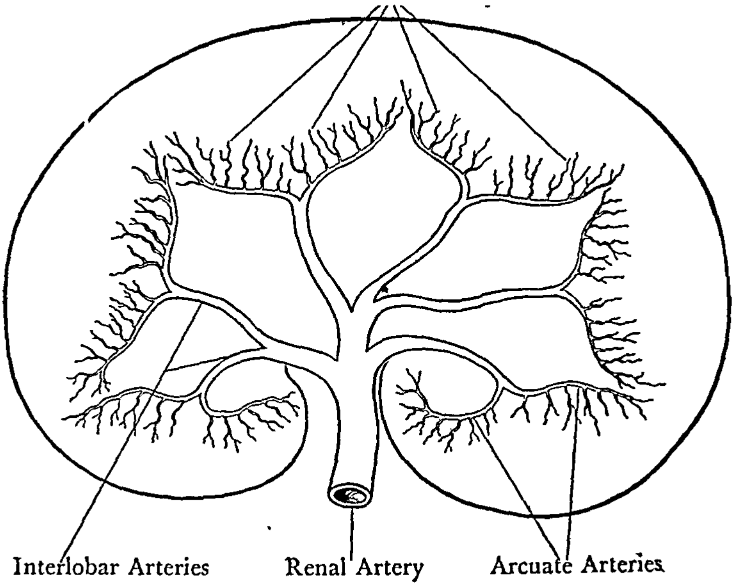

FIG. 1.6. Main branches of the renal arterial tree illustrating that the arcuate arteries are only connected by a capillary anastamosis.

penetrate straight into the cortex, where they give rise to short afferent glomerular arterioles, so that even the most distal glomerulus receives its afferent arteriole direct from a relatively large artery. The smooth muscle of the afferent arteriole ceases as the arteriole joins the area of the juxtaglomerular apparatus. Beyond the glomerulus the blood flows into the efferent arteriole and then into a capacious intercommunicating plexus of capillaries situated between the tubules (the peritubular venous capillaries) which empties into the interlobular veins (Fig. 1.7). The endothelial cytoplasm of the peritubular venous capillaries has the same electronmicroscopic appearance as that of the endothelial cells in the glomerular capillaries. It contains multiple round areas approximately 600 Å wide in which the thickness of the cytoplasm is reduced to 70 Å, an arrangement which must facilitate the transport of substances to and from the blood

The blood supply to the medulla passes through those glomeruli which are nearest to the medulla, these are sometimes known as juxtamedullary glomeruli Their blood supply is quite different from other glomeruli Instead of the blood flowing through an afferent arteriole which enters the glomerulus breaks up into capillaries and then emerges as an efferent arteriole, the afferent and efferent arteriole form *one large continuous vessel which contains smooth muscle throughout* and in which there is little evidence of renin secretory activity The lumen into the glomerular capillaries opens directly on one side of this arteriole in such a way that a proportion of the blood which flows to the medulla does not pass through glomeruli (Fig 1 7)

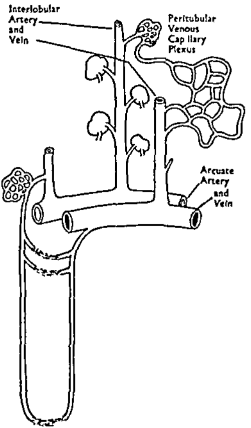

Fig 1 7 Schema illustrating the renal circulation of the cortex and medulla

The blood to the medulla courses through two distinct systems. One consists of compact bundles of long tubes of capillary thickness which carry the blood down to, and away from, the apex of the pyramids; these are the descending and ascending vasa recta. The other system consists of a thick network of fine capillaries, it is situated in the outer half of the medulla; the same area as that occupied by the thick parts of the ascending limbs of the loop of Henle. The venous blood from the medulla empties into the arcuate veins. The striking feature of the medullary circulation is that the blood in the long bundles of vasa recta is forced to flow in a counter-current fashion. It follows that the vasa recta with their capillary-like walls not only act as conduits for blood, but because the blood within them is in equilibrium with the interstitial fluid, there is imposed upon the environment of the medulla the physical properties of a counter-current system (p. 42).

The Interstitial Space

The cortex is almost free of connective tissue and in an ordinary histological preparation the peritubular venous capillaries and the tubules are contiguous, which suggests that there is no interstitial space. It is by no means certain however that this is true in life. Sections from kidneys which have been frozen instantaneously, after being excised from living animals, show that there exists a clear area around each tubule, between the tubule and the peritubular capillary. It is also well established that the blood that drains from a kidney which has just been excised from a living animal has a much lower hæmatocrit than the hæmatocrit of that animal's arterial or venous blood. It is probable that the extra plasma lies in the clear areas around the tubules. Usually these spaces are not visible, for the plasma they contain escapes with the blood in the capillaries via the cut renal artery and vein.

The presence of an interstitial space in the medulla is certain, for the many parallel tubes that it contains are separated by a lagging of connective tissue which is particularly thick towards the apex of the pyramids.

The Juxta-Glomerular Apparatus

In each nephron the first part of the distal tubule rises from the medulla and comes to lie near the glomerulus of that nephron (Fig. 1.8). At this point the afferent arteriole to the glomerulus is in close contact with the distal tubule. The area where this contact takes place is called the juxta-glomerular apparatus for here the cells of the afferent arteriole contain cytoplasmic secretory granules of renin, and the distal tubular cells next to these granular cells are columnar with their nuclei placed near the lumen of the tubule. In the space between these specialised arteriolar and tubular cells there lies a third type of cells

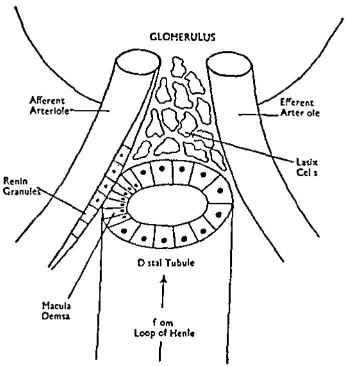

FIG 1 8 Schema of juxtaglomerular apparatus

which form a lace work pattern known as lacis cells, they also extend into the intercapillary area of the glomerulus and resemble mesangial cells Electron microscopy studies suggest that the granular cells of the arteriole, the lacis cells and the intercapillary cells of the glomerulus are related to each other and to smooth muscle

Renal Nerves

The innervation of the kidneys comes from both the sympathetic and the vagus via the splanchnic nerves The sympathetic supply is usually from T6 to T12 Within the renal parenchyma there is a widespread distribution of nerves and it is possible to trace nerve fibres until they reach and envelop the tubules as well as the capillaries There are no ganglia in the kidney

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2

TESTS OF RENAL STRUCTURAL INTEGRITY

The following methods are used to obtain information about the structure of the kidney

- Clinical Examination of the Abdomen
- *Straight X-ray of the Abdomen*
- Intravenous Pyelography
- Renal *Tomogram*
- Renal Scintigram
- *Retrograde Pyelography*
- Renal Arteriogram
- Renal *Biopsy*
- Isotope Renogram

Clinical Examination of the Abdomen

Obviously this is most helpful in thin patients and may give information about the presence of a tumour hydronephrosis and polycystic kidneys, if the kidneys are readily palpable it is usually easy to decide whether or not they are much larger than normal To obtain the best results from this examination it is essential that the patient move his diaphragm well down with each inspiration, while relaxing the anterior abdominal muscles Some patients seem unable to do this, but may be taught to do so by being told to place their hands palm downwards on the surface of their abdomen while they practice Tenderness in the renal angle or over the kidney anteriorly indicates that there is inflammation which may be due either to infection infarction or an allergic reaction

A distended bladder is often an invaluable clue to the presence and cause of renal failure

Straight X-ray of the Abdomen

Such an X ray is less revealing than an intravenous pyelogram but it has certain advantages It can be performed at short notice and it causes no discomfort Often the outline of the kidneys may be distinguished so that their size, shape and position can be determined and it may also be possible to decide whether there are any shadows consistent with the presence of calculi or renal calcification

Intravenous Pyelography (I.V.P.)

This is achieved by the rapid intravenous administration of sodium diatrizoate (Hypaque) or sodium acetrizoate (Diaginol) at a time when the rate of urine flow is minimal. These two substances consist of dense molecules containing three radio-opaque iodine atoms which are filtered through the glomerulus and also secreted into the tubular fluid by the proximal tubules. In practice the amount which passes through the glomeruli far exceeds that secreted by the tubules. When there is a considerable concentration of these substances in the tubular fluid the renal parenchyma becomes faintly visible, while their presence in the urine causes the calyces, pelves and ureters to be densely shadowed.

Intestinal gas and movements, fæces and fat may considerably obscure and confuse the results. An aperient should be taken the preceding evening and, if it has failed to act, a small enema should be given. It is best to allow the patient to be up and about for 24 hours before the examination, and a low-residue diet and no medicine containing bismuth or similar radio-opaque substances should be taken for at least two days previously. Intestinal gas can sometimes be dispelled by an injection of aqueous vasopressin or neostigmine methylsulphate.

The density of the pelvic shadow is dependent upon the following:

(1) The concentration of sodium diatrizoate or acetrizoate in the blood perfusing the glomeruli.
(2) The number of glomeruli.
(3) The rate of urine flow, or in other words, the volume of urine in which the radio-opaque substances are contained.
(4) The antero-posterior depth of urine through which the X-rays have to penetrate.

The optimum concentrations in the blood are obtained with 60 to 100 ml. of 60 per cent sodium diatrizoate. Larger quantities increase the amount in the tubular fluid, but because of the accompanying osmotic diuresis their opaqueness to X-rays may be reduced. Nothing can be done to increase the number of nephrons, but it is probable that noxious stimuli (see below), including perhaps the radio-opaque substances themselves may decrease the function of the nephrons by renal vasoconstriction.

To increase the amount and depth of the urine in the pelves and ureters they are sometimes forcibly distended by partially obstructing the lower ureters by compression of the lower abdomen with an inflatable rubber balloon. This is best done about 5–10 minutes after the injection of the contrast solution, when its concentration in the pelves has reached a plateau The rate of urine flow is reduced as much as possible by fluid deprivation or the administration of vasopressin tannate in oil

The main value of an I V P is that it demonstrates the size and configuration of the pelves and calyces, it is helpful in determining the size, shape and position of the kidneys, it is particularly useful in first suggesting that there may be unilateral parenchymal disease Occasionally distortion of a calyx is best seen on a lateral or oblique view If the radio-opaque substance is given rapidly and films are taken at 15 sec, 1, 2 and 3 min intervals after the injection, additional information can be obtained which is useful in the detection of those occlusions of the renal arteries which are sufficient to cause hypertension, this manœuvre must be performed without ureteric compression

Though the excretion of the contrast medium in easily visible radiological concentrations gives a relatively good indication that renal function is not grossly impaired, it is important to note that a poor or absent I V P shadow does not necessarily indicate abnormal renal function

Obviously if one kidney is completely destroyed or if the number of nephrons in one or both kidneys is inadequate to excrete the contrast medium at a sufficient rate to produce a visible concentration a poor or absent shadow is an indication of failing function But absent or faint shadows on one or both sides occur too frequently with normal kidneys to be accepted as anything but a tenuous suggestion of abnormality and if there is no confirmatory evidence of abnormality from other sources, the I V P should be repeated Occasionally there may be no shadow during the first I V P, yet a normal shadow is seen a few days later during a second The reason for such anomalies is not always clear Occasionally they are due to a transient hypotension or ureteric obstruction It is also possible that the apprehension and discomfort, which are an unavoidable part of intravenous pyelography, may sometimes be responsible The patient has to remain in one position on a hard X ray table for a considerable time and for some of this time he may endure a severe compression of the lower abdomen Much less stress is known to cause a brisk rise in urine-flow from inhibition of anti diuretic hormone secretion, or an osmotic salt diuresis (p 115)

An I V P should not be performed in patients suffering from myeloma particularly if there is any degree of renal failure. They may develop irreversible acute renal failure from precipitation of proteins in the collecting ducts Otherwise renal failure with a raised blood urea is not a contraindication to the performance of an intravenous pyelogram. In most cases, however, it provides little or no useful information for there is an insufficient quantity of radio-opaque substance in the urine.

Renal Tomograms

This technique is most useful when a patient presents with advanced renal failure of unknown cause. A renal tomogram enables one to determine the size and position of the kidneys with little disturbance to the patient. It is then easier to decide whether the renal failure is the end stage of a disease which has gradually destroyed the kidneys or an acute episode developing in previously normal kidneys.

Renal Scintigram

After the administration of an Hg^{203} labelled diuretic, the mercurial salt and its label enter the cells of the proximal tubule where it remains for a certain time. It is then possible to delineate the outline of the kidneys by scanning the renal areas with a scintillation counter. The technique does not disturb the patient. Its main use is in finding out the position of the kidneys, detecting major differences in outline and size and in picking up local areas of renal disease when they are of sufficient size, such as tumours, cysts and areas of infarction. It is sometimes useful in detecting small amounts of viable kidney tissue which have not been revealed by any other tests.

Retrograde Pyelography

A radio-opaque solution is introduced directly into the pelvis of the kidney after cystoscopy and ureteric catheterisation. Sodium diatrizoate (25 per cent) or sodium acetrizoate (15 per cent) is injected under considerable pressure to distend the pelvis and ureter; this is done after the patient has recovered from the anæsthetic so as to avoid overdistension.

The information to be derived from a retrograde pyelogram is obviously confined within the borders of the pelvis, calyx and ureter.

Renal Arteriography

A radio-opaque substance is injected directly into the abdominal aorta at a point just above the origin of the renal arteries; 20–30 ml. of 70 per cent diodone or 30 ml. of 50 per cent sodium acetrizoate are administered via a catheter introduced through a femoral artery; the total volume is administered in four seconds. The fluid travels rapidly into the renal arteries, capillaries and veins. Exposures are made at intervals of a few seconds following the injection at a time when tubular secretion of diodone is relatively insignificant It is a highly specialised technique which gives good pictures of the renal vascular tree Its greatest use is to identify localised obstructions of the renal artery and its main branches It can also reveal the presence of anomalous arteries and is sometimes most useful in defining the existence of localised areas of disease in the renal parenchyma, and distinguishing between tumours and cysts The tumours being vascular become radio-opaque in contrast to the cysts which do not cast a shadow One of the advantages of this technique is that it enables information to be obtained about the substance of the kidney when an intravenous pyelogram has failed to produce a shadow Serious complications are rare, but include acute renal failure To obtain good pictures of the vessels in the cortex it is necessary to introduce the dye through a catheter which has been threaded from the aorta directly into the renal artery

Renal Biopsy

A renal biopsy can be performed in two ways Either the biopsy needle can be inserted through the intact skin when the biopsy sample is then obtained ' blind " Or the biopsy needle is inserted into the kidney under direct vision through a deep formal surgical approach in the patient's flank There is little doubt that in centres where renal biopsies are performed infrequently it is probably safer, and a satisfactory sample of renal tissue is more likely to be obtained more frequently, if the biopsy is performed under direct vision This technique has the additional advantage that hæmorrhage into the perirenal tissues can be prevented On the other hand in order to perform an open biopsy the patient has to be anæsthetised and he has to suffer the discomforts and possible complications of an abdominal operation

In most centres, therefore where renal biopsies are frequently needed it is customary to use the blind technique The biopsy is usually performed in the prone position Some authorities prefer to have the patient in an operating theatre where it is certainly more convenient for the operator A general anæsthetic is rarely given unless the patient is particularly nervous or very young A sand bag is placed under the abdomen, or if the patient is on an operating table, the bridge is raised The kidney is usually found by reference to a previously performed intravenous pyelogram, though sometimes a straight X ray of the abdomen is sufficient A fine exploring needle is inserted through the renal angle and the structures down to the kidney infiltrated with local anæsthetic When the needle is thought to be near the kidney the patient is asked to hold his breath the syringe containing the local anæsthetic is disconnected from the needle and the patient is now asked to take one or two deep breaths. The needle is probably in the kidney if that portion of the needle outside the skin swings through a wide arc with each respiration. This is sometimes misleading if the patient is fat or œdematous and it must be remembered that the needle will also swing if it is in the liver. Whether or not the needle swings, it sometimes rotates on its long axis on respiration. This is an almost certain indication that it is in the kidney. The fine needle is then withdrawn and the procedure repeated with the biopsy needle when an attempt is then made to bring a fragment of the kidney to the surface.

Experience greatly improves performance. Apart from the recurring difficulty of bringing the piece successfully to the surface, there are certain patients who present special difficulties. For instance, those with extensive spinal deformities such as spondylitis deformans or lumbar scoliosis, and those with ascites or pregnancy. There is general agreement that the contraindications to renal biopsy are (1) the presence of only one kidney, (2) a tendency to bleed, and (3) the presence of a hypernephroma, a large renal cyst, a perinephric abscess, or hydro- or pyonephrosis, and (4) an uncooperative patient. Some workers would also include a high blood urea (greater than 100 mg./100 ml.), and malignant hypertension, unless the blood pressure is controlled during and for a few hours after the biopsy is performed. If the patient is being treated with an artificial kidney it is usual not to do a biopsy for two or three days on either side of a dialysis because of the heparin which is used during the dialysis.

After the biopsy the patient is placed on his back and told to remain in that position uninterruptedly for at least 12–18 hours. This is more likely to produce hæmostasis than reliance on a tight abdominal bandage. The patient is also given a large drink of water to induce a diuresis. This not only diminishes the possibility of clot formation if there is hæmaturia but more quickly demonstrates its presence and extent. The serious complications of biopsy are preponderantly those of hæmorrhage either into the renal pelvis or into the retroperitoneal space. Microscopical hæmaturia always occurs, and direct observation of the retroperitoneal tissues during an open renal biopsy also shows that there is always a perirenal hæmatoma. It is generally considered, however, that a " complication " has occurred only when either the hæmaturia is macroscopic, particularly if there is clot formation, or if the retroperitoneal hæmorrhage is sufficiently large to cause pain in the flank and a fall in hæmoglobin. Gross hæmaturia occurs in about 5–10 per cent of cases, and perirenal hæmatoma in about 2 per cent. Occasionally macroscopical hæmaturia persists for several days, and there are a few instances of a delayed onset of hæmaturia. Blood transfusions have been used in about 2 per cent of cases. Other complications include pain during the biopsy which is usually in inverse relationship to the patient s nervousness A sharp but unimportant pain is produced if the ileoinguinal nerve is transfixed as it emerges from the border of the sacrospinalis, while a dull ache radiating into the iliac fossa indicates that a retroperitoneal hæmorrhage is forming A few patients complain of a transient pain in the back after the biopsy Comparisons of renal functional capacity before and after the biopsy have demonstrated that unless there is ureteric obstruction from a clot there is no disturbance of function Serial renal aortograms have been performed in a few patients after renal biopsy They have revealed a disturbing number of transient intrarenal arterio-venous shunts which may take several months to resolve

A renal biopsy is clearly the only method of making an exact histological diagnosis during life The information which has been obtained in this way has been of the greatest value in throwing light upon the natural course of renal disease It is true that often such diagnostic precision is of no therapeutic benefit to the patient and that the histological appearance may frequently be surmised from the history clinical details and past experience of autopsy material nevertheless even in the present era of therapeutic helplessness in regard to most renal diseases there are occasions when an exact histological diagnosis may be of importance in deciding the patient s future treatment

Isotope Renogram

Para amino-hippuric acid (PAH) is actively secreted by the proximal tubules into the tubular fluid and it is then excreted in the urine (p 82) If a single injection of I^{131} labelled PAH is given intravenously the concentration of PAH in the kidney rises within a minute to a peak and then falls gradually to control values in the next 10 to 20 min If a scintillation counter is placed over the kidney and the intensity of radiation emitted from the I^{131} labelled PAH in that area is continuously monitored it is possible to obtain a continuous graph of this process. The shape of the curve will clearly depend on (i) the rate at which the PAH reaches the kidney i e the renal blood flow (ii) the number and condition of proximal tubule cells which transport the PAH into the tubule fluid and (iii) the rate at which the PAH is carried away from the kidney in the tubular fluid and urine The technique is most useful in detecting and particularly in following the course of ureteric obstruction It is also useful in following the progress of a transplanted kidney At one time the isotope renogram was used extensively to try and detect localised abnormalities of the renal circulation such as renal artery stenosis For this purpose, however, it should never be used as the only screening procedure, it should be one of a battery of tests for it is liable to give false negative results in up to 25 per cent of patients with renal artery stenosis.

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3

INTRODUCTION TO RENAL FUNCTION AND SOME THEORETICAL CONSIDERATIONS CONCERNED IN TESTING ITS INTEGRITY

The function of the kidney is to assist in keeping the volume and composition of the extracellular fluid within normal limits, it is also concerned with the maintenance of a normal blood pressure and erythropoiesis

The composition and volume of the extracellular fluid is controlled by glomerular filtration, and tubular reabsorption or secretion In a day approximately 180 l of almost protein free fluid is filtered through the glomerular capillaries into the glomerular space, from whence it passes into the tubule As this filtrate travels down the tubule various *substances are either subtracted or added to it, so that eventually* only about one litre emerges as urine, this is the water and solutes which the body needs to discard. The renal mechanisms involved in regulating the blood pressure and erythropoiesis are obscure, they are discussed in Section 9 (p 104) and Section 10 (p 107)

In normal circumstances every glomerulus is continuously being perfused with blood, there is no evidence that the intermittency of glomerular circulation described in the frog is present in man The rate of blood flow is adjusted by alterations in the afferent and efferent *glomerular arterioles Such changes must influence the glomerular* capillary pressure and in turn the rate of glomerular filtration Alterations in glomerular filtration rate are, within wide limits affected by changing the rate of filtration in each glomerulus There is no evidence that new nephrons are opened up when glomerular filtration rate increases, and complete closure of some glomeruli only occurs when glomerular filtration rate is suddenly reduced below 50 per cent

Normally approximately 120 ml of filtrate are separated from the 600 ml of plasma that pass through the kidneys each minute The *ratio glomerular filtration rate renal plasma flow is known as the* filtration fraction It can be seen that in health it is about 0 2 In disease it may vary from 0 1 to 0 3, but it is clear that, as might have been expected, the relationship between the rate of renal plasma flow and the glomerular filtration rate remains relatively close.

Glomerular filtrate contains all the diffusible ultrafiltrate substances present in plasma and, ignoring a slight difference caused by the plasma proteins, they are present in the same concentrations. There is also some indirect evidence that the filtrate contains small concentrations of protein, probably less than 30 mg./100 ml.; though this is a relatively insignificant concentration, it nevertheless amounts to a filtration of about 50 g. of protein in 24 hours.

Theoretical Considerations

The contents of the urine are selected from the plasma by a wide variety of mechanisms. It follows that the methods used to measure the efficiency of these mechanisms also vary. For instance, it will be shown in Section 5 that one of the best methods for testing the kidney's ability to control the sodium content of the extracellular fluid is to place the patient on a salt-free diet, and then to observe whether the kidney is able to diminish the excretion of sodium. Such a method is obviously unsuitable for measuring the kidney's ability to control the extracellular fluid concentration of substances which, regardless of intake, are continuously being manufactured by the body, e.g. urea and creatinine.

It has been found empirically that the most convenient gauge of the kidney's ability to control the extracellular fluid concentration of substances such as urea and creatinine is to calculate the quotient

$$\frac{\text{amount excreted in the urine per min.(mg./min.)}}{\text{concentration in the plasma (mg./ml.)}} \text{ or } \frac{UV}{P}$$

where U = the concentration in the urine (mg./100 ml.), V = the urine volume per min. (ml./min.), and P = the plasma concentration (mg./100 ml.). This quotient can of course be calculated for any substance which is present in the plasma and the urine, but it is of no value if the result is greatly influenced by factors unrelated to renal function (e.g. diet). It is useless, for example, to calculate the quotient for sodium for in a normal person it may vary by more than 100 per cent during a single day. The quotients for urea and creatinine, however, are relatively constant for their urinary excretion throughout the day is far more uniform.

The quotient $\frac{UV}{P}$ is inevitably expressed as ml./min. (i.e. $\frac{\text{mg./min.}}{\text{mg./ml.}} = \text{ml./min.}$) and is conventionally referred to as a " clearance." This curious term derives from an extension of the fact that the result of dividing the amount excreted in the urine by the plasma concentration gives the least volume of plasma which could have contained the amount excreted. It follows that the quotient can therefore be considered as representing the volume of plasma which must be completely ' cleared " to provide the amount appearing in the urine The concept of a clearance is only a particular way of thinking about the quotient $\frac{UV}{P}$, it is obviously unrelated to what is actually happening in the kidney, for there is no evidence that some of the plasma is stripped of certain of its contents while the remainder emerges unchanged The disadvantages of the word ' clearance ' are the tortuous explanations and frequent misconceptions to which it gives rise

Measurement of Glomerular Filtration Rate

The most precise measurement of glomerular filtration rate is obtained with inulin, for after passing freely through the glomerulus it travels down the tubule without any being subtracted or added by the tubule cells The quantity that is excreted in the urine in one minute is therefore the same as that which is filtered But it is known from puncture of the glomerular capsule by micropipettes that the capsular fluid (i e the glomerular filtrate) is identical to plasma ultrafiltrate Therefore the quantity of inulin present in the urine must, as it passes through the glomerulus be accompanied by a quantity of water sufficient to keep the inulin concentration in the capsular space the same as in the plasma This volume is clearly that of the glomerular filtrate, it is estimated by calculating the least volume of water (i e plasma) that can have contained the amount of inulin excreted in the urine, i e $\frac{UV}{P}$ The inulin clearance is thus a measure of glomerular filtration rate For instance, if the plasma concentration of inulin is 10 mg /100 ml , and 10 mg of inulin is excreted in the urine in one minute, it is clear that if inulin is not reabsorbed or secreted by the tubule cells, 100 ml of water passing through the glomerular filter in one minute

For similar reasons the creatinine clearance is also used as a measure *of glomerular filtration rate, but it is not so exact as inulin for a small* quantity of creatinine is secreted into the tubular fluid by the tubules.

Measurement of Renal Plasma and Blood Flow

The renal plasma flow (R P F) can theorectically be calculated by the Fick principle using any substance excreted in the urine, provided that the renal arterial (RA), and renal venous (RV) plasma concentrations, the urine flow (V), and the urine concentration (U) of that substance are known

$$\text{R P F (ml /min)} = \frac{\text{UV (excretion per minute)}}{\text{RA-RV (arterio venous difference)}}$$

From this renal blood flow (R.B.F.) can be calculated from the arterial hæmatocrit (Hct):

$$\text{R.B.F.} = \frac{\text{R.P.F.}}{1 - \frac{\text{Hct}}{100}}$$

It will be seen below that this laborious procedure is seldom necessary, but it can be performed by obtaining samples of arterial blood from the femoral artery, while renal venous blood is obtained via a catheter introduced through an antecubital or femoral vein.

Clearly a substance that is almost completely excreted by the kidney and therefore has a large RA–RV difference will give more accurate results than one like sodium which has an insignificant RA–RV difference. An almost ideal substance is para-amino-hippuric acid (PAH) which is infused intravenously until a steady plasma concentration is achieved.

If the plasma PAH level is less than 5 mg./100 ml. about 90 per cent of the PAH reaching the kidney is promptly excreted in the urine (except in cases of advanced renal failure). In general, therefore, it is not necessary to catheterise the renal vein to sample the renal venous blood, for it can be assumed that RV is negligible (i.e. RV = 0) or:

$$\text{R.P.F.} = \frac{\text{UV}}{\text{RA}}$$

In other words the clearance of PAH is a measure of renal plasma flow.

Furthermore, since the *peripheral* venous plasma concentration of PAH is almost identical to that in the arterial blood, it is also unnecessary to sample arterial blood, and the whole technique is greatly simplified.

In clinical work PAH clearances are hardly ever estimated. There is a relatively rigid relationship between the renal blood flow and the glomerular filtration rate, and it is easier to estimate filtration rate than renal blood flow. The simplest way to perform a PAH clearance is to inject 12 ml. 20 per cent PAH mixed with 6 ml. 2 per cent xylocaine into the loose subcutaneous tissues of the axilla. The urine collection periods are begun 30–45 minutes later.

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4

TESTS OF GLOMERULAR FUNCTIONAL INTEGRITY

It has been mentioned earlier that approximately 600 ml of plasma pass through the glomeruli per minute from which are filtered about 120 ml of fluid that is almost free of protein and blood cells Glomerular integrity can thus be studied by measuring glomerular filtration rate and by examining the urine for the presence of protein, cells and casts

Glomerular Filtration Rate

The four methods most widely used to obtain an indication of the glomerular filtration rate are, in descending order of accuracy

1. Inulin clearance
2. Vitamin B_{12} clearance
3. Creatinine clearance
4. Urea clearance
5. Plasma concentrations of creatinine and urea

Inulin Clearance

An inulin clearance is a protracted procedure, many blood samples are needed and, as urine is collected at short intervals, relatively large errors due to incomplete bladder emptying may occur which can only be avoided with certainty by catheterisation For these reasons glomerular filtration rate, except for research purposes, is hardly ever determined by inulin clearance For clinical purposes an inulin clearance can most easily be performed after an intravenous injection of 90 ml of 10 per cent inulin The urine collections are begun 30 minutes later

Vitamin B_{12} Clearance

In physiological amounts vitamin B_{12} is firmly bound to plasma proteins If, however, the binding sites on the proteins are saturated by the administration of large amounts of vitamin B_{12} a proportion of the vitamin will then be in a free or dialysable state The clearance of this dialysable vitamin B_{12} is the same as that of inulin, and vitamin B_{12} *can therefore be used to measure glomerular filtration rate* Radioactive vitamin B_{12} (^{57}Co-Cyanocobalamin) is given after the plasma protein binding sites have been saturated with stable vitamin B_{12}

In this way all but about 8 per cent of the plasma radio-active vitamin B_{12} is free and the clearance of vitamin B_{12} is technically easy. Unfortunately, the extent of protein binding cannot be assumed to be the same from patient to patient and it must therefore be estimated each time. This is a time-consuming and not altogether satisfactory business. The only advantage a vitamin B_{12} clearance had over an inulin clearance was that it substituted an easy isotopic counting technique (vitamin B_{12}) for a protracted manual chemical estimation (inulin). Now, however, that inulin can be estimated on an automatic analyser this advantage no longer exists and in view of the difficulties with plasma binding, a vitamin B_{12} clearance is now the more laborious technique.

Creatinine Clearance

This remains by far the most convenient method of obtaining a fairly accurate estimate of glomerular filtration rate. The clearance of pure creatinine however is slightly greater than that of inulin, indicating that some creatinine is actively secreted by the tubules. For clinical purposes this is unimportant; except in a few patients who are excreting large amounts of protein in the urine when the creatinine to inulin clearance ratio may rise to two. In addition patients with advanced renal failure may have ratios as high as 1·4, but at these low rates of glomerular filtration such errors are of no great moment. Urine and plasma creatinine are now estimated on an automatic analyser. In this way the original technical difficulties inherent in trying to distinguish between pure creatinine and the other plasma chromogens are avoided.

The clearance of creatinine is a much more convenient determination to make than that of inulin, for creatinine is already present in body fluids; its plasma concentration being remarkably steady throughout the 24 hours. Creatinine clearance tests can therefore be performed over long periods without the necessity of continuous intravenous administration; and because the plasma concentration is so constant only one sample of blood need be taken for a 24-hour collection of urine. Such long periods minimise inaccuracies caused by incomplete bladder emptying or slipshod timing of the duration of urine collection; they also diminish the effect of transient emotional reactions on renal function.

Procedure for a 24-hour Creatinine Clearance

The basic requirements are a 24-hour collection of urine and one sample of blood taken at any time during this period. But because an accurately timed collection of urine is so incredibly difficult to obtain, it is perhaps worth while describing some of the difficulties which are encountered A 24 hour collection of urine can start at any convenient hour e g 9 a m at this time the patient is asked to empty his bladder and this urine is discarded for the next 24 hours all the urine that is passed is collected into one container and the collection ended when the patient is asked to empty his bladder for the last time at about the same hour as on the previous day this urine being included in the 24 hour collection It is clearly of no importance if the actual duration of the collection period is a few hours more or less than 24 so long as it is accurately timed The volume of the urine is then *measured and the rate of urine flow per minute is calculated by dividing* this volume by the number of minutes which the collection period has lasted A convenient slogan is that the urine collection should be timed to the nearest minute and measured to the nearest ml A screw topped bottle full of this urine and the blood sample are then sent together to the laboratory for creatinine estimation and calculation of the clearance

This simple manœuvre may be vitiated by the following accidents (1) Unless the patient has been warned urine may be passed during defæcation and thrown away (2) unless urine is placed immediately into a large container it may be lost and not included in the 24-hour collection (3) occasionally the urine passed at the beginning of the collection period is included in the total collection though the patient may have four or *five hours urine in his bladder* (4) it is not unknown for a 24 hour collection to cease when the container into which it is *being collected is full regardless of the time the collection began* beware therefore of a 24 hour collection bottle filled to the brim Many of these troubles can be avoided by making the patient responsible for his own urine collection

Urea Clearance

The clearance of urea is the most widely used test of renal function its value depends on the fact that urea clearance is directly related to the glomerular filtration rate As a guide to the rate of glomerular filtration however it is inferior to the creatinine clearance Its main disadvantages are (1) The clearance of urea is considerably less than the rate of glomerular filtration (2) this discrepancy varies with the rate of urine flow and (3) the ward procedure involved in a urea clearance makes it very vulnerable to technical inaccuracies

In normal subjects when the urine flow is greater than 2 ml /min urea clearance is about three-fifths of the glomerular filtration rate at lower urine flows it is less This relationship is illustrated in Fig 4 1 It suggests that though there is every reason to believe that urea is filtered through the glomerulus at the same rate as inulin and creatinine, for urea is a small highly diffusible molecule, a great deal must be reabsorbed as it passes down the tubule. At urine flows above 2 ml./min. the amount reabsorbed is constant and is about two-fifths of the quantity which has been filtered, and as the urine flow becomes less so gradually more urea is reabsorbed. In an average man, therefore, the urea clearance at urine flows above 2 ml./min. is $3/5 \times 120 = 75$ ml./min.; such a clearance (obtained at urine flows greater than 2 ml./min.) is sometimes called the maximum urea clearance. For traditional reasons this absolute figure is sometimes converted into a

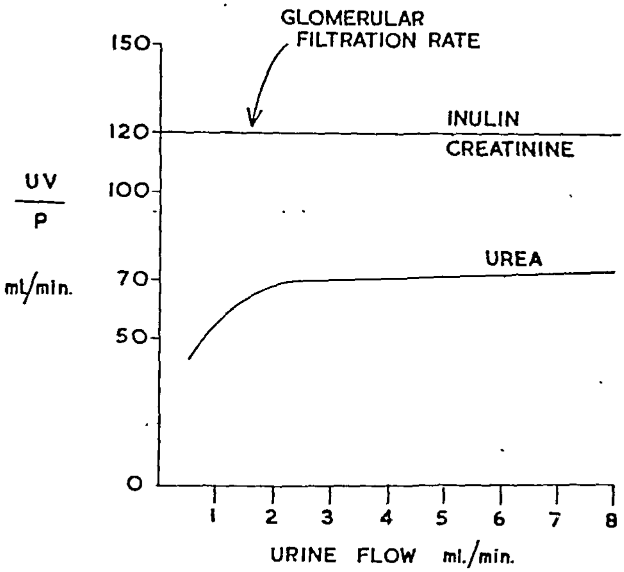

FIG. 4.1. Schema showing the relationship between the clearances of inulin, creatinine and urea to the urine flow and to each other.

percentage, i.e. a urea clearance of 37 ml./min. is reported as being $\frac{37}{75} \times 100 = 50$ per cent of normal. The merit of this system is that one does not have to remember the normal urea clearance, but why this dispensation to feeble memories should be extended to urea clearance is not certain. It probably dates from the time when clinicians were considered to be unable to grasp absolute figures.

When the urine flow is less than 2 ml./min. urea clearance varies with the rate of urine flow, but in normal subjects, if the clearance is then multiplied by the square root of the rate of urine flow, a figure is obtained which approximates to an average of 54 ml./min., regardless of the rate of urine flow. This mathematical jugglery is called a "standard urea clearance", it is a manœuvre which adjusts all the true clearances measured at rates of urine flow below 2 ml /min as if they had been estimated at a standard urine flow of 1 ml /min The results are again expressed as a percentage This rigmarole has probably caused more confusion about the nature of renal function in those not familiar with the subject than any other of the many mathematical obscurities which so often enshroud the kidney It is obvious that a "standard urea clearance" is *not* a clearance and that the use of the word "standard" in this context is misleading For clinical purposes these complications are best avoided by doing urea clearances at rates of urine flow above 2 ml /min

Procedure or Urea Clearance

Plasma levels of urea may fluctuate, and urea clearances vary with *the urine flow, so that clearances have to be performed over short* periods It is customary to perform them in the morning when the patient is in a fasting state In order to raise the urine flow above *2 ml /min two glasses of water are given about half an hour before the* beginning of the first period when the bladder is emptied and the urine discarded An hour later the bladder is emptied again, the urine is *saved and a sample of venous blood is taken Finally the urine is* collected once more after a further hour The volume of the two urine collections is measured and a sample of each collection is then sent, *together with blood to the laboratory for urea estimation and calcula*tion of the clearance The point of having two collection periods is to enable a comparison to be made between these two clearances so that *the accuracy of the urine collection may be gauged*

Serious errors will occur if the bladder cannot be emptied properly or if those concerned with noting the duration of the urine collection period are horologically amoral Occasionally the *test may be in*fluenced by the emotional reactions of the patient to having to empty his bladder at predetermined intervals, or to having to submit to venepuncture

There is a point in the laboratory technique which sometimes causes confusion The urea clearance is usually expressed as a "blood" clearance, i e $\frac{UV}{B}$ (as opposed to $\frac{UV}{P}$) This is possible because urea is freely diffusible into red cells and the concentration of urea in whole blood is almost identical to its concentration in plasma Blood urea estimations can therefore be performed on spun red cells leaving the supernatant plasma available for other estimations

Plasma Concentrations of Urea and Creatinine as a Guide to the Rate of Glomerular Filtration

Normal plasma urea concentrations vary between 15–35 mg. per 100 ml., the lower values tending to be found principally in children, and during pregnancy: normal plasma creatinine concentrations vary between 0·15–1·4 mg. per 100 ml. If the clearance of these substances parallels the rate of glomerular filtration it is clear that when the filtration rate falls their plasma concentrations will rise. It would seem simpler therefore, when trying to gauge the state of the glomerular filtration rate, to be guided by an estimation of these plasma concentrations instead of having to perform clearances. Unfortunately the relation between glomerular filtration and plasma concentration is such that these concentrations are only of limited usefulness in this respect. The reasons for this are given below.

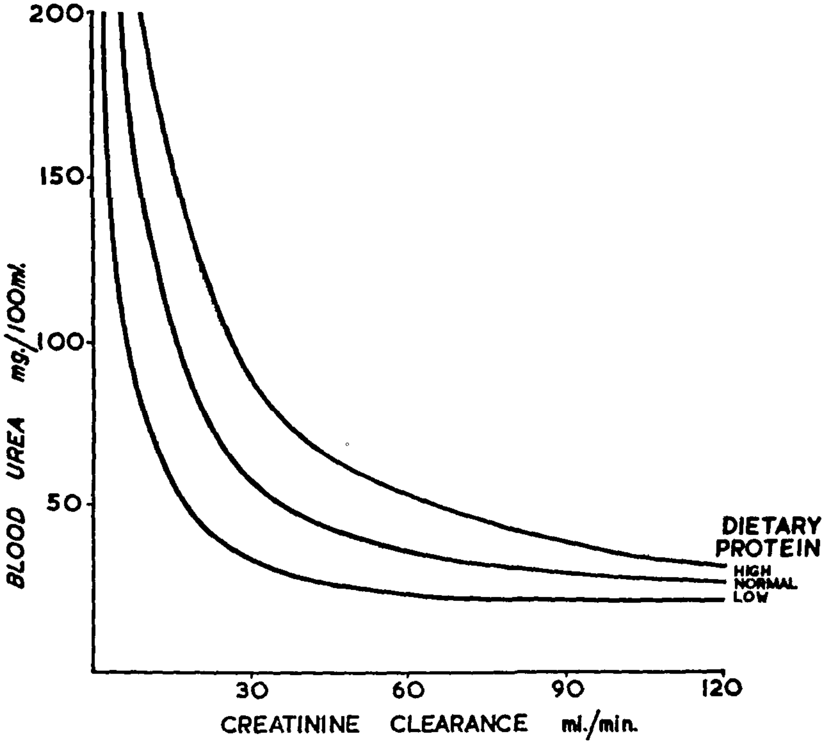

FIG. 4.2. Schema of the relationship between glomerular filtration rate (creatinine clearance) and the blood urea at varying levels of protein intake.

The plasma concentrations of urea and creatinine depend on their rate of production and elimination. If their route of elimination is via the glomerular filtrate and their daily production is relatively constant, then a fall in glomerular filtration rate will cause their plasma concentrations to rise until a new equilibrium is reached Conversely, if *glomerular filtration rate remains constant* and the rate of urea or creatinine production increases their plasma concentrations will also increase The connection between glomerular filtration, the production of urea and creatinine, and their plasma concentrations are analogous to the situation that obtains when fluid is being poured into a funnel *The height of the level of the fluid in the funnel depends on the diameter* of the funnel's outlet and the rate at which the fluid is being delivered into the funnel The level rises until it has become sufficiently high above the outlet to force the fluid out as fast as it is being poured in at the top If the outlet is then partially occluded or the rate of delivery into the funnel is increased the level of fluid in the funnel rises higher until a new equilibrium is reached The supply of liquid into the funnel represents the production of urea and creatinine the height of liquid in the funnel their plasma concentrations, and the diameter of the outlet the rate of glomerular filtration When each new equilibrium is reached the rate of elimination equals the rate of production

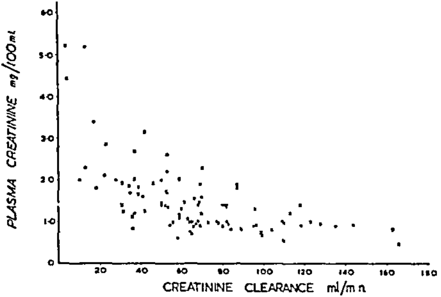

Fig 4 3 The relationship between plasma creatinine concentration and the creatinine clearance in 140 patients. It can be seen that at any one clearance the plasma creatinine concentrations are widely scattered For instance there are several clearances below 50 ml /min with normal creatinine concentrations (i e below 1·4 mg /100 ml)

The relationship between the blood concentration of urea and the glomerular filtration rate is illustrated in Fig 4 2 It can be seen that as the glomerular filtration rate diminishes there is at first only a small absolute rise in blood urea so that when the filtration rate is down to half its normal value the blood urea is still only 35–50 mg. 100 ml. Further reductions in filtration rate, however, produce large absolute changes.

The implications behind this relationship are: (1) Plasma concentrations of urea and creatinine show little absolute change until, functionally, the patient has lost one kidney; (2) when the glomerular filtration rate is low a small additional reduction in filtration rate will produce large changes in plasma concentrations. The latter is particularly striking in a patient with a moderate degree of renal failure and a blood urea of 50–60 mg. per 100 ml. who develops cardiac failure, or who has a hæmorrhage; the blood urea may then rise to 150–200 mg. per 100 ml. with a superimposed decrease in glomerular filtration rate of only 10–20 ml./min.

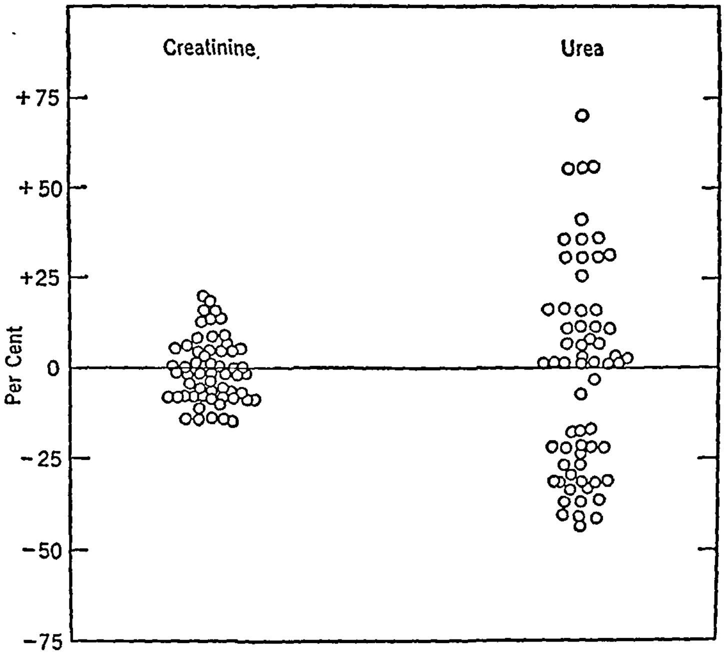

FIG. 4.4. Serum concentration of creatinine and urea. The percentage variation from the average serum concentrations of creatinine and urea in normal men on diets containing 0·5 to 2·5 g. of protein per kg. body weight. It is apparent that the creatinine concentrations vary less than those of urea. (Addis, 1949, "Glomerular Nephritis," Macmillan, New York.) See also Fig. 4.5 (p. 31).

It is clear that if the blood urea concentration is greater than 60 mg. per 100 ml., or the plasma creatinine above 2 mg. per 100 ml., there is probably severe depression of glomerular filtration rate; but values below these are indifferent indications of glomerular function (Fig. 4.3). This is not only because at these lower concentrations large disturbances of glomerular filtration cause small absolute changes in plasma concentrations but also because such small changes may be due to other factors than alterations in filtration rate This is particularly applicable to urea for (1) its rate of elimination in the urine is not only related to the glomerular filtration rate but also to the urine flow, and (2) its rate of production is profoundly affected by dietary protein con*tent and endogenous protein catabolism Fig 4 2 illustrates the effect* of high and low protein diets on the relation between blood urea and glomerular filtration rate in normal subjects It shows that with low protein intakes the level of blood urea may remain within the normal *range though there is a substantial fall in glomerular filtration rate* (the impaired production of urea in liver disease may also cause a similar effect) Fig 4 5 illustrates this point in a patient with advanced renal failure (creatinine clearance of 5 ml /min) Conversely, a high protein diet will raise the blood urea to pathological levels though the glomerular filtration rate is normal or unchanged These factors also influence the plasma concentrations of creatinine but to a much smaller extent (Fig 4 4) for the rate of creatinine production is mainly a function of the size of the muscle mass and is little influenced by protein intake

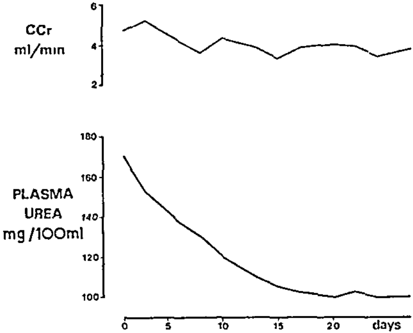

FIG 4 5 The effect of a 20g protein diet on the blood urea and creatinine clearance in a patient suffering from advanced renal failure There is a profound fall in blood urea though there has been a slight fall in creatinine clearance

Finally, plasma concentrations of both urea and creatinine are often misleading because they lag behind changes in glomerular filtration rate. This is most obvious during the first few days of acute renal failure when there may be a gross reduction in glomerular filtration rate with initially a relatively small rise in blood urea or creatinine.

Conclusion

In a patient in whom renal disease is suspected the finding of a substantial rise in blood urea or creatinine is nearly always good evidence of a severe reduction in glomerular filtration rate. If the patient has been on a low protein diet however, an estimation of the plasma concentration of urea may be grossly misleading (e.g. blood urea of 70 mg. per 100 ml. with a glomerular filtration rate of 10 ml./min.); in these circumstances the creatinine concentration permits a much more accurate assessment of the filtration rate. With plasma concentrations in or near the normal range it is necessary to estimate a 24-hour creatinine clearance or a one-hour urea clearance before it can be decided whether there is any impairment of filtration rate.

The only advantage of a urea clearance is that when the glomerular filtration rate is below approximately 10 ml./min., then an accurate urea clearance estimated over a short, collection period is close to the inulin clearance regardless of the rate of urine flow. In addition, an abnormally low urea/inulin clearance ratio indicates an increased back diffusion of urea through damaged tubules.

Proteinuria

It is probable that glomerular filtrate contains 10–20 mg. per 100 ml. of protein, and that the relative lack of protein in the urine is due to its being reabsorbed by the tubules. The normal 24-hour protein excretion is 0–90 mg. In theory, therefore, the presence of protein in the urine means either that an increased amount has escaped from the glomeruli or that less has been reabsorbed by the tubules. But though diminished tubular reabsorption may occur, proteinuria is usually due to changes in the glomeruli.

It is best to test for proteinuria by precipitation either by boiling or by the addition of salicyl sulphonic acid. " Stick " tests such as Albustix do not detect Bence Jones protein (p. 362) and should therefore not be used in a ward. The normal low protein concentration of the urine is not apparent with these tests; otherwise they are relatively delicate and with 25 per cent salicyl sulphonic acid a protein concentration of 0·2 g./l. is evident as a " trace," and 5·0 g./l. will give a heavy flocculent precipitate. For clinical purposes it is traditional to comment on the proteinuria in a semiquantitative manner, a barely perceptible precipitate being called a "trace" and a heavy precipitate ++++, with + to +++ in between This is more useful if the concentration (i e specific gravity) of the urine is measured at the same time for the rate of protein excretion is relatively constant throughout the 24 hours and is related to the glomerular filtration rate whereas the concentration of protein fluctuates with urine flow In other words, the finding of + of protein in a dilute urine indicates a much greater rate of protein loss than a similar finding in a concentrated urine The only accurate way to measure the extent of proteinuria is to measure the amount of protein excreted in 24 hours

In general one may say that persistent proteinuria does not occur with disease of the lower urinary tract, neoplasms of the urinary tract, however, will sometimes give rise to intermittent or persistent proteinuria, and with severe exudative or hæmorrhagic lesions there may be protein +, but this will only occur when the pus and blood are visible macroscopically It is essential to realise that it is the presence of protein in the urine which is the important abnormality, and that the rate of protein excretion is of secondary importance Advanced renal failure may be associated with only a trace of protein in the urine Proteinuria is almost always present when there is disease of the renal parenchyma, and though there are many transient and unimportant causes of proteinuria, it should not be dismissed, particularly if it is persistent In women a trace of protein may be caused by contamination with vaginal discharge

Starch electrophoretic separation of urinary proteins distinguishes some of the proteins being excreted They are the same as those present in the plasma, although their relative concentrations are different, for their rate of urinary excretion seems to be related to molecular size The loss therefore, of albumin and α_1 globulin is usually much greater *than that of α_2 globulin, a distribution which is characteristic in the* nephrotic syndrome Occasionally the pattern may be different, in acute nephritis the urinary proteins are in the same proportions as those in the plasma while in myelomatosis a small globulin may appear without albuminuria The pattern of protein excretion is best measured quantitatively by distinguishing the proteins either by specific immunochemical techniques or by their molecular weights on a Sephadex G 200 column

Urinary Deposit

Red and white cells and hyaline casts are found in normal urine *In order to determine accurately the extent of white and red cell* excretion it is necessary to measure their rate of excretion per unit time

The subject empties his bladder as completely as possible, the time is carefully noted, and the urine discarded. Three to fours hours later, the bladder is emptied once more, the time again noted and the urine kept. In women it is necessary to avoid including cells from the urethra and introitus. The urine is therefore collected in two containers. The concentration of cells is measured only in the urine that is excreted into the second container; the rate of excretion is then calculated by multiplying this concentration by the total volume, i.e. the volume of urine in both containers. In men it is only necessary to avoid preputial contamination. Within two hours the specimen is thoroughly shaken, precipitated phosphates dissolved by adding a few drops of glacial acetic acid, and 10 ml. is measured into a graduated centrifuge tube. After spinning at 2,000 r.p.m. for five minutes, 9 ml. of the supernatant is discarded and the remaining 1 ml. thoroughly mixed with a Pasteur pipette. The cells in a drop of this fluid are then counted in 2 c.mm. of the ruled area of a Fuchs-Rosenthal counting chamber under 1/6 objective. Only unequivocal polymorphs are counted, disrupted and degenerated cells are not included. The results are calculated as follows, and expressed either as the number of red cells or the number of leucocytes cells excreted per hour.

$$N = \frac{500 \times C \times V}{10\,T} = \frac{50\,CV}{T},$$

where C = actual number of cells counted, V = volume of specimen in millilitres, T = time in hours over which the specimen was formed, and 500 = the factor to convert 2 c.mm. to 1 ml. The cells are more easily recognised if the urine is not too concentrated; it is useful therefore, to see that the patient passes about 200–400 ml. of urine in the three to four hours of the collection period.

With this technique an excretion of white cells greater than 200,000 per hour is abnormal; the average normal excretion is about 50,000 per hour with a range of 0 to 200,000/hr. though occasionally normal subjects have rates between 200,000 and 400,000/hr. The rate of excretion of red cells is approximately the same. This is a relatively laborious technique which again suffers from those recurrent difficulties which are associated with trying to obtain a timed sample of urine. It has been found, however, that a close approximation to the red or white cell excretion rate can be obtained by simply measuring the *concentration* of red or white cells in a drop of uncentrifuged urine (Fig. 4.6). Again a counting chamber is used but it is not necessary to time the urine collection or to spin the urine. When there are more than 10 white or red cells per c.mm. the white or red cell excretion rate is abnormally high, whereas if there are less than three per c.mm. it is normal; when the result lies between three and 10 per c mm. it is best to repeat the test. These criteria apply to children and adults; in infants less than 10 white cells per c.mm. is considered to be normal.

There are two other ways in which the white cell content of the urine has been gauged in the past. One consisted of anecdotal remarks *such as "scanty white cells", "a moderate number of white cells"* and the now famous "white cells seen". This technique is only of use when the white cells are very numerous. In the other method a sample

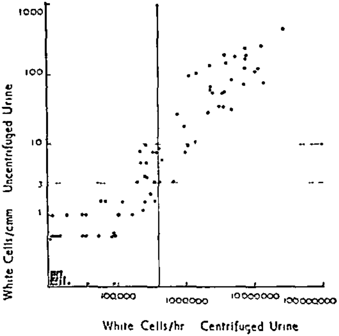

FIG 4 6 Comparison of the white cell concentration measured in uncentrifuged urine (white cells per c mm) with the white cell excretion rate calculated from counts made on centrifuged urine (white cells per hr) *The vertical line is at 400 000 cells per hr. The horizontal line at 3 and* 10 cells per c.mm. (Little, *Brit. J. Urol*, 1964)

of urine is spun for 10 min., a drop of the deposit is then placed on a plain glass slide and covered by a cover slip. The numbers of cells seen per high power field (usually with a 1/16 objective) is then reported. *Fig. 4.7 compares the number of white cells seen per high power field in* each of 155 urines against the white cells excretion rate. It is clear that this technique is only useful when there are more than five cells seen *per high power field when it can be safely assumed that there is a high* urinary excretion of white cells. When there are less than five cells per high power field the excretion rate may be normal or raised. As this technique is more complicated and less reliable than the one in which a drop of unspun urine is examined in a counting chamber there is no good reason why it should linger.

It is important to note that there is a misleading relationship between the colour of the urine and the concentration of red cells it contains. For instance, frank hæmaturia, i.e. the macroscopic appearance of red cells in the urine sufficient to cause an acid urine to be brown or an alkaline urine to be red, is produced by only 0·2 ml. of blood in 500 ml. of urine.

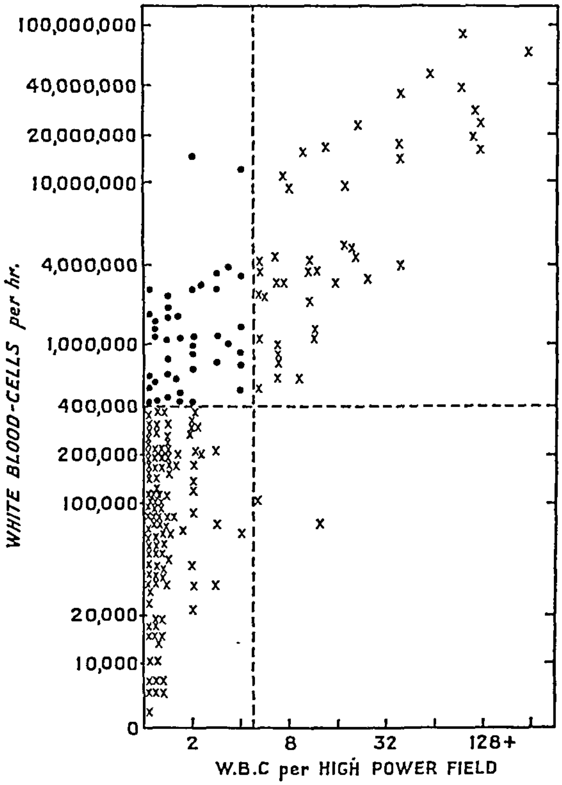

FIG. 4.7. Urinary white cell excretion rate compared with the number of cells seen per "high power field" examination of the same urines. The horizontal line is at 400,000 cells per hr; the vertical line is at 5 cells per "high power field". ● = urine with high w.b.c. excretion but with less than 5 cells seen per "high power field". (Little, *Lancet*, 1962).

Many different types of casts may be seen—blood, granular, hyaline waxy and broad—the most important diagnostically being granular and blood casts. All are basically formed by the precipitation of a mucoprotein secreted by the tubule into which are imbedded the red cells which are leaking through the diseased glomeruli, or the degenerated tubule cells which are flaking off the walls of the nephron.

Hyaline casts are transparent, without any cells attached to their surfaces; they are of no importance clinically. Blood casts are characterised by a diffuse orange-yellow colour which is the hæmoglobin from hæmolysed red cells; these casts tend to break into short stumpy rectangular masses which are easily overlooked. Granular casts contain either relatively intact red cells or desquamated tubular cells. The highly significant fact about blood and red cell granular casts is their indication, beyond any shadow of doubt, that the hæmoglobin and red cells they contain must have originated from the renal parenchyma and not from the lower urinary tract

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5

TUBULAR FUNCTION AND TESTS OF TUBULAR FUNCTIONAL INTEGRITY

THE functions of the tubule are to reabsorb, or prevent the reabsorption of the contents of the tubular fluid, and to secrete into the tubular lumen substances which are either circulating in the peritubular venous capillaries or which are formed by the tubule cell. These processes are under the control of a wide variety of hormones, plasma electrolyte concentrations and gas pressures.

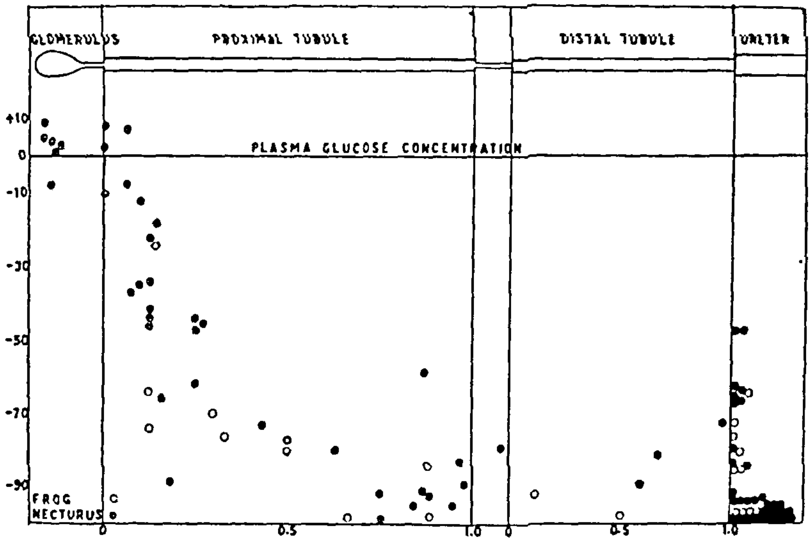

FIG. 5.1. Site of glucose reabsorption. Chart showing differences in glucose concentration between plasma and fluid collected with a micropipette from various levels of the renal tubules of normal Necturi and frogs. Zero on the ordinate represents plasma, figures above and below zero represent percentage differences from plasma. (Walker and Hudson, 1937, *Amer. J. Physiol.*)

The principal function of the proximal tubule is to reabsorb about 80 per cent of the total solids and water from the glomerular filtrate. The solids are reabsorbed in unequal proportions so that while proteins and glucose, for instance, appear to be almost completely reabsorbed (Fig. 5.1), sodium chloride is only partly reabsorbed, and there is little or no reabsorption of urea and creatinine. This reabsorption takes place in such a way that the fluid in the proximal tubule always remains isotonic to arterial blood. The *p*H of the fluid, however, may change, and when the urine is acid the process of acidification begins in the proximal tubule (Fig 5 2) The main function of the loop of Henle is to make the interstitial fluid in the medulla *hypertonic* and the tubular fluid that emerges from it *hypotonic* these changes permit the concentration of the final urine to be modified over a wide range (see below) As a result there flows into the distal tubule a hypotonic tubular fluid containing considerable quantities of sodium chloride and waste products with a *p*H which is much the same as that in the fluid emerging from the proximal tubule. The principal functions of the distal and collecting tubules are to adjust the *p*H osmolality and electrolyte content of this fluid and to prevent or impede the reabsorption of the waste products

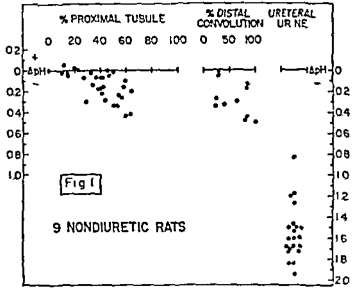

Fig 5 2 Localisation of urine acidification in the rat kidney The points show the difference in *p*H of the tubular fluid obtained in various parts of the nephron or the ureter from that of arterial blood Points below the horizontal line = *p*H below that of plasma. Note that the fluid begins to be acidified in the proximal tubule but that the main increase in acidity occurs between the distal tubule and the ureteric urine i.e in the collecting tubule (*Gottschalk Lassiter and Mylle 1960 Amer J Physiol*)

The following tubular functions will be discussed

1 Water excretion
  (*a*) Urine concentration
  (*b*) Urine dilution and water elimination
2 Hydrogen ion excretion
  (*a*) Bicarbonate excretion
  (*b*) Titratable acid and ammonia excretion
  (*c*) Urine *p*H

3. Sodium and chloride excretion.
4. Potassium excretion.
5. Calcium excretion.
6. Magnesium excretion.
7. Phosphate excretion.
8. Amino-acid excretion.
9. Uric acid excretion.
10. Maximal tubular capacity to reabsorb glucose and secrete PAH.

WATER EXCRETION

The kidney's ability to modify the rate of urine flow is largely responsible for the constancy of the volume and osmolality of body fluids; and the rate of urine flow is mainly determined by the tubule's ability to control the concentration of the urine. In the following account the terms *hypertonic, isotonic* and *hypotonic* refer respectively to osmolalities which are greater than, equal to, and less than those of plasma. Osmolality can be defined as the concentration of particles in a solution. The highest urine concentration attainable is about 1,300 m.osmole/kg. H_2O (S.G. 1·040) which is about four times greater than the concentration of plasma, approximately 300 m.osmole/kg. H_2O (S.G. 1·008), while the lowest concentration is about 50 m.osmole/kg. H_2O (S.G. 1·001).

The osmolality of the urine is mainly dependent on two interlocking factors, (i) the functional integrity of the loop of Henle, and (ii) the concentration of circulating antidiuretic hormone (ADH). The loop of Henle produces a *hypotonic* tubular fluid (Fig. 5.3) and a hypertonic interstitial fluid. Fig. 5.4 illustrates how this takes place. The ascending thick limb of the loop of Henle which is persistently impermeable to water transfers sodium chloride (and perhaps urea) actively from its lumen into the interstitial fluid. The tubular fluid within the lumen thus becomes hypotonic and the interstitial fluid hypertonic. In addition the descending streams of fluid within the thin descending loop of Henle, and the capillary-like vasa recta (p. 7), both of which are in osmotic equilibrium with the interstitial fluid, greatly increase this hypertonicity so that it becomes maximal towards the tip of the papillæ. This effect is most easily understood if it is considered as a series of successive steps which tend to trap the sodium chloride in the interstitial fluid of the medulla. As the descending isotonic fluid (300 m.osmole/kg. H_2O) first enters the area into which the ascending thick limb is pumping out sodium it becomes slightly hypertonic (e.g. 350 m.osmole/kg. H_2O). The next step repeats the first. The now slightly hypertonic fluid continues downwards, and again more sodium

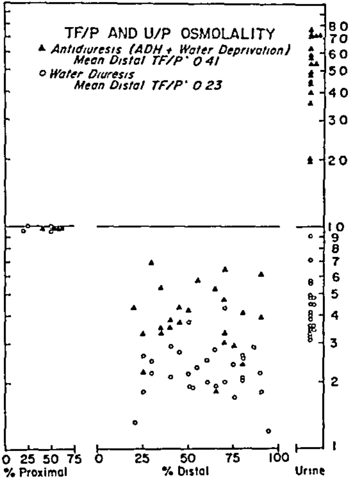

FIG 5 3 Site of dilution and concentration of the urine in the dog Each *triangle or circle represents the results obtained in a sample of tubular* fluid removed by micropuncture The site of each micropuncture is represented along the horizontal axis as a percentage of the length of the proximal or distal tubule. The tubular fluid or urine/plasma osmolal ratio is indicated along the vertical axis. At the horizontal line 1 0 the tubule fluid is isosmotic with the plasma, above this line the fluid or urine is hypertonic, and below the line the fluid or urine is hypotonic. ▲ = results in dehydrated dogs, O = results in dogs having a water diuresis It can be seen that the tubular fluid in the proximal tubule is always isosmotic whereas in the distal tubule it is always hypotonic whether the urine is hyper- or hypotonic In the dehydrated animal the osmolality of the distal fluid is about 150 m Osm /kg (plasma = 300 m Osm /kg/H_2O) whereas in the dogs having a water diuresis it is approx 75 m Osm /kg /H_2O) (Clapp and Robinson, 1966, *J clin Invest*)

and chloride is added to it by the ascending thick limb of the loop of Henle. There is therefore another rise in the osmolality of the fluid, but this time from slightly hypertonic (350 m osmole/kg. H_2O) to slightly more hypertonic (e g. 400 m osmole/kg H_2O). By a succession of such steps the osmolality at the tip of the papillæ may rise to 1,300 m.osmole/kg. H_2O. This phenomenon is known as a counter current multiplier. The osmolality of the medullary fluid is always hypertonic but the extent of this hypertonicity varies with the osmolality of the urine. When the urine is hypotonic it falls to approximately 400 m.osmole/kg. and when the urine is hypertonic it rises to the same level

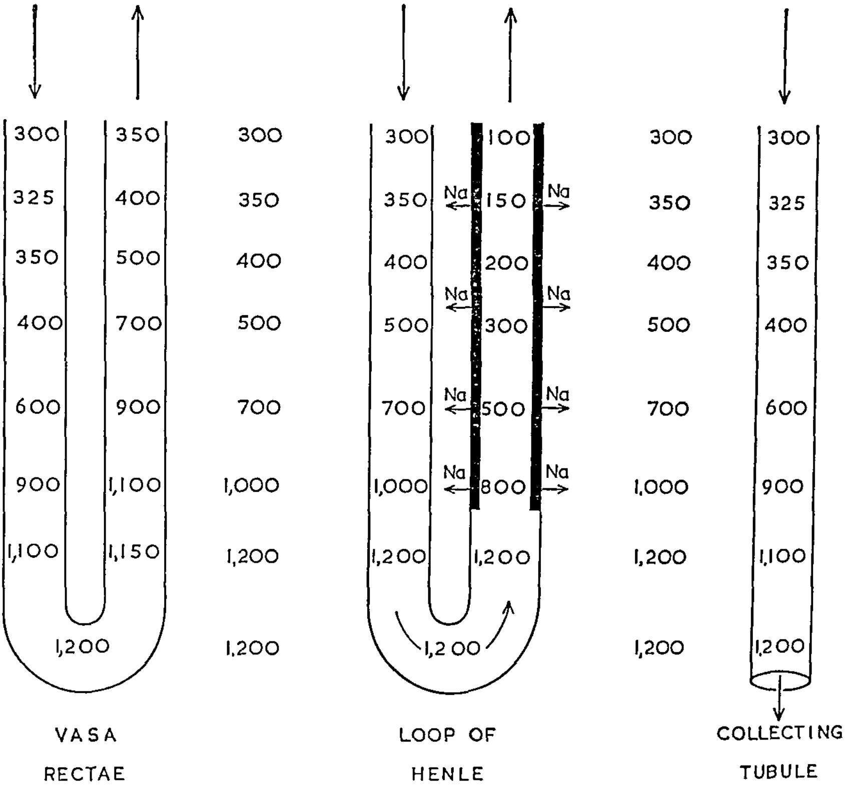

FIG. 5.4. Mechanism of urine concentration. The diagram illustrates the counter-current multiplier of the loop of Henle and the counter-current exchanger of the vasa rectæ (p. 7). The first is responsible for the rise in medullary interstitial fluid osmolality, and the second ensures that this hyperosmolality is not dissipated by vascular irrigation.

as that of the urine, i.e. to a maximum of around 1,300 m.osmole/kg. (for mechanism see p. 44).

When the plasma ADH concentration is low, following a drink of water or disease of the neurohypophysis, the urine is hypotonic and is excreted in large volumes, and when the ADH concentration is raised following dehydration the urine is hypertonic and only small amounts are excreted. ADH alters the concentration of the urine by changing the " permeability " of the distal and collecting tubule; the presence of

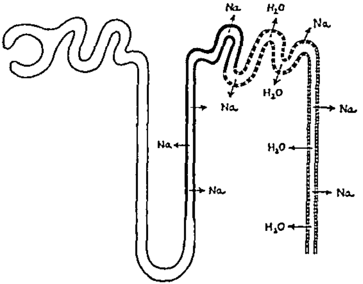

FIG 5 5 Mechanism of urine concentration. Diagram of a nephron during the excretion of a hypertonic urine. Thick lines indicate sites where it is probable that the tubule wall is always relatively impermeable, and the lattice lines where, in the presence of antidiuretic hormone it becomes permeable. The effect of the antidiuretic hormones on the permeability of the distal tubule is less marked than on the collecting duct (see FIG 5 3)

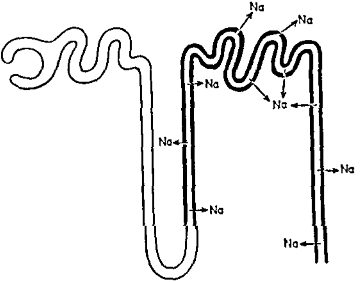

FIG 5 6 Mechanism of urine dilution Diagram of a nephron during the excretion of hypotonic urine Thick lines indicate relative impermeability of the tubule wall It is probable that most of the ascending limb of Henle and the first part of the distal tubule are always relatively impermeable whereas the wall of the second part of the distal and the whole of the collecting tubule only become permeable in the presence of antidiuretic hormone (de Wardener, 1960, *J Chron Dis*)

ADH causing the " permeability " to increase. In this way when ADH is absent the " impermeability " of the distal and collecting tubules is intact, the hypotonic fluid which continuously emerges from the loop of Henle then remains hypotonic as it travels down, and hypotonic urine is excreted. This phenomenon is aided by the simultaneous fall in the osmolality of the interstitial fluid which occurs when the concentration of circulating ADH is low.

When ADH is present and the " permeability " of the distal and collecting tubule is increased, the hypotonic fluid which emerges from the loop of Henle tends to come into osmotic equilibrium with the interstitial fluid on the other side of the tubule wall. As the fluid passes along the distal tubule therefore, where it is surrounded by the isotonic interstitial fluid of the cortex, it becomes less hypotonic and its volume is much reduced, but it is still hypotonic (150–200 m.osmole/kg.) when it leaves the distal tubule (Fig. 5.5). In the collecting duct where the interstitial fluid of the medulla is hypertonic this reduced volume of moderately hypotonic fluid from the distal tubule becomes hypertonic, and hypertonic urine is excreted (Fig. 5.6).

All the evidence suggests that the " permeability " of the distal and collecting tubule also controls the passive reabsorption of urea from the tubular fluid and that this in turn influences the concentration of the urine. In the absence of ADH, when the urine is hypotonic, the reabsorption of urea is at its lowest and the excretion of urea is at its highest; whereas in the presence of ADH, when the urine is hypertonic, the movement of urea out of the tubular fluid into the hypertonic medullary interstitial fluid is at its highest, and the excretion of urea is at its lowest. The counter-current of fluids within the vasa recta and loop of Henle tends to trap the urea within the medulla (in the same way that it traps the sodium chloride) so that the concentration of urea rises towards the tip of the papillæ, a mechanism known as a counter-current exchanger (Fig. 5.7). This increases the osmolality of the medullary interstitial fluid and more water is then reabsorbed from the fluid in the collecting ducts. The osmolality of the urine then rises by an amount equal to the urea concentration in the medullary interstitial space. It follows that one of the factors responsible for the kidney's increased capacity to concentrate the urine on a high protein diet is the increased excretion of urea that then occurs.

In addition to its effect on the tubule's permeability to water and urea ADH has also been shown to increase the rate of active sodium transport in isolated membranes such as frog skin. If ADH has the same effect on the ascending limb of the loop of Henle it is possible that the increase in the hypertonicity of the medulla, which occurs when there is a rise in the concentration of circulating ADH, is due not only to its effect on the tubule's permeability to urea but also to an increased delivery of sodium into the medullary interstitial fluid

It is intuitively understandable that the counter-current exchanger phenomenon of the vasa recta is likely to be more efficient at relatively low rates of blood flow *It is interesting therefore that when ADH is* present and there is a need for as high a medullary interstitial fluid osmolality as possible, the flow of blood through the vasa recta is reduced This is probably due to the constricting effect on the vasa recta of the rise in the interstitial fluid osmolality, caused by the effect *of ADH on urea and possibly sodium transport*

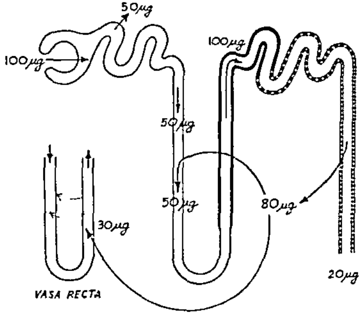

Fig 5 7 Schema of the trapping of urea in the medulla during hypopenia. Of each 100 µg of urea that is filtered at the glomerulus 50 µg is reabsorbed *in the proximal tubule The remaining 50 µg* passes *down into the loop* of Henle where it is joined by 50µg which has come from the collecting ducts 100 µg therefore goes into the distal tubule and collecting duct 80 µg diffuses out of the collecting duct into the interstitial space and 20 µg is excreted in the urine 30 µg of the 80 µg which diffuses out of the collecting duct is removed from the kidney by the vasa recta. (Diagram based on findings of Ullrich *et al* 1963 *Amer J Physiol*)

Methods Used to Measure the Concentration of the Urine

It is customary to measure the concentration of the urine by its specific gravity, which is an indication of the weight of the solutes in *solution* The kidney's capacity *to concentrate however, is related to* the concentration of particles in solution (i.e. the osmolality*) and not to their weight. This fact is most easily demonstrated by measuring the specific gravity of urine following an intravenous pyelogram when values of S.G. 1·060 may be found. Such values are much greater than any obtained following dehydration and are due to the excretion of large heavy molecules of radio-opaque substance; the particle concentration of such urine is within normal limits.

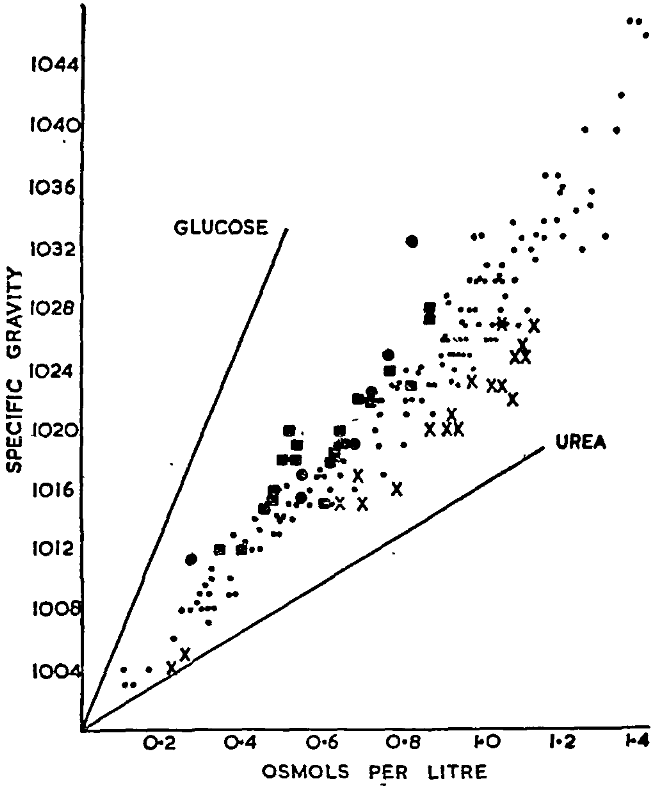

FIG. 5.8. Relationship between specific gravity and osmolality of urine. Different urines are shown as follows: with no sugar or protein (O), with + + + sugar (●), with + + + protein (■), after 25 g. urea by mouth (X). Lines are also given showing the relationship between specific gravity and osmolality of glucose and urea solutions. (Miles and de Wardener, 1954, *Brit. med. J.*)

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* The osmolality of a solution is an index of the number of particles it contains in 1 kg. of water, whereas the osmolarity of a solution is an index of the number of particles contained in 1 litre of the solution. In biological fluids the two are very similar. Determinations of freezing point and vapour pressure measure osmolality, i.e. m.osmole/kg. H_2O. Some years ago some of us failed to appreciate these facts and the term osmolarity was used when osmolality was measured. This explains why some of the diagrams in these pages, which have been taken from earlier papers mention osmolarity and m.osmole/l. instead of osmolality and m.osmole/kg. H_2O. It should be noted that in this context the symbol H_2O is often omitted, and osomolality described as m.osmole/kg.

The concentration of particles, i e the osmolality of a solution, may be calculated from a determination of its freezing point or vapour pressure These techniques are laboratory procedures, and it is fortunate that when urine contains only normal constituents, the correlation between *specific gravity and osmolality is sufficiently close for* specific gravity to be used as a clinical guide to the osmolality of the urine *This relationship is illustrated in Fig 5 8, which also shows that* if urine contains much glucose the specific gravity will be greater at a fixed osmolality, than in normal urine, and, conversely, if the urine contains much urea (a less dense molecule) the specific gravity will be lower

Clinical hydrometers are convenient but relatively coarse instruments with which to measure specific gravity, it is important therefore that they should be used with care In order to check incorrect graduations clinical hydrometers should always be tested in water each time they are used, and, to avoid surface tension errors on the stem, the hydrometer should be spun and plunged well into the urine Detergents should not be used for cleaning urine bottles or specimen glasses, for these lower surface tension and increase the measured specific gravity *And the specific gravity should never be measured* in freshly passed warm urine, for hydrometers are standardised at a *temperature of 16° C , for every 3° C above this temperature the* specific gravity will appear to be 0 001 less than its true value, i e if a hydrometer is placed in urine at 37° C and shows a reading of 1 013, the true specific gravity is 1 020 An adjustment is also necessary when there is gross proteinuria, 0 001 is subtracted for every 5 g /l of protein

Procedure Used to Test the Tubule's Ability to Concentrate Urine

This test can be performed by depriving the patient of fluid or by giving an injection of vasopressin tannate in oil Before doing either, the specific gravity of a sample of urine passed on waking should be measured, *for if such a random sample is greater than 1 018 it is most* unlikely that the maximum concentration achieved by fluid deprivation or vasopressin administration will be below normal

Fluid Deprivation Fluid deprivation results in a rise of plasma osmolality and a shrinkage of the extracellular volume, both changes which are known to increase antidiuretic hormone production The urine becomes concentrated but often does not approach its maximal value for 24–36 hours (Fig 5 9) This is rather a long time to dehydrate patients and a convenient clinical compromise is to do the test over a period of 24 hours as follows The period starts at 8 a m when the intake of all fluid, including ice creams, soups and fruit, ceases until

8 a.m. of the following day. The concentration of all urine samples passed during the last 12 hours of this period is estimated, and one of these should equal or be greater than S.G. 1·022. The normal range of urine concentration obtained with this procedure varies from S.G. 1·022 to S.G. 1·040. The highest figures are rarely seen in persons over the age of 20. Occasionally an apparent inability to concentrate is due to the test being performed during a diuresis caused by the spontaneous (and sometimes induced) excretion of œdema fluid.

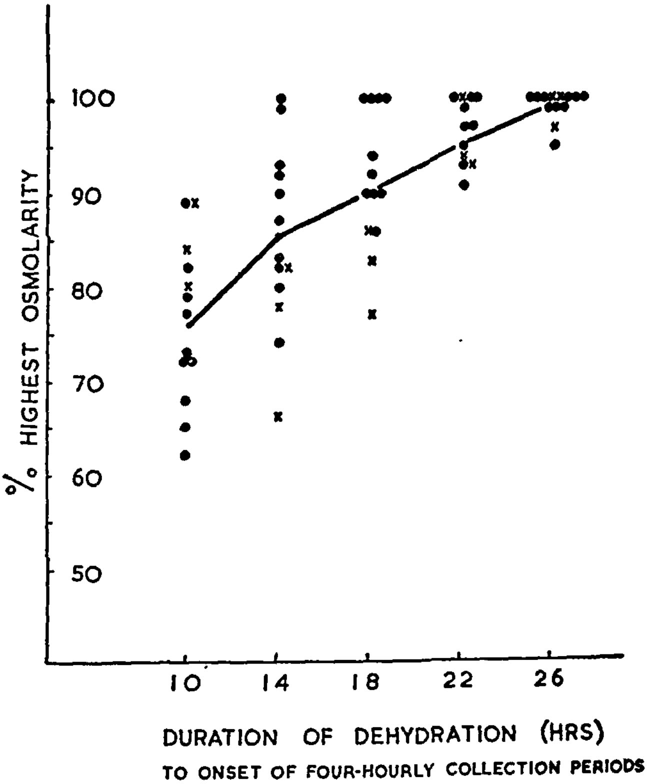

Fig. 5.9. The effect of progressive water deprivation on the urine osmolarity in 13 subjects. The osmolarity is expressed as a percentage of the highest osmolarity reached in each subject during 30 hours fluid deprivation. Urines were collected between 8 a.m. and 4 a.m. in cases marked with a dot, and between 8 p.m. and 4 p.m. in those marked with a cross. (Miles and de Wardener, 1954, *Brit. med. J.*)

Fluid deprivation is nearly always unpleasant for the patient, and occasionally, if a severe negative fluid balance develops because of an inability to concentrate, the test may even be dangerous. The test should always be terminated if the loss of body weight exceeds 4 per cent. For these reasons the test is hardly ever repeated, which greatly lowers its value. The test may also be vitiated by the patient's emotional reactions to having his kidneys " tested " and it may induce him to have an emotional diuresis

Vasopressin* Tannate in Oil Fluid deprivation and its discomforts and disadvantages can be avoided by giving instead an injection of vasopressin tannate in oil Theoretically one might expect the concentration of the urine to be the same whichever method were used In practice the concentration following vasopressin is slightly less than after fluid deprivation, but for clinical purposes this is not important, as the discrepancy between the two techniques gradually becomes smaller as the ability to concentrate diminishes (Fig 6 10)

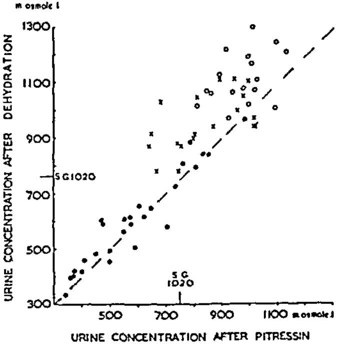

Fig 6 10 Osmolarity of urine after 36–48 hours deprivation of fluid compared with that following an injection of vasopressin tannate in oil in 62 persons (○) healthy persons (X) patients convalescent from non renal disease (●) patients with renal disease The diagonal line shows where the points would lie if deprivation of fluid and vasopressin tannate concentrated the urine equally (After de Wardener 1950 *Lancet*)

The test is best performed by combining a short period of fluid deprivation and an injection of vasopressin Fluid deprivation begins at 6 p m , at 8 p m an injection of 5 units of vasopressin tannate in oil is given subcutaneously and at 10 p.m. the bladder is emptied. Fluid deprivation ceases at 10 a.m., or sooner if the patient is distressed by thirst. Vasopressin should be used in infants with care, the large quantities of milk they normally imbibe can easily cause water intoxication.

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* Vasopressin *is the name given to the antidiuretic substance obtained from the* neurohypophysis of animals after death there is no evidence that it differs from antidiuretic hormone (ADH) the substance secreted by the neurohypophysis during life *Pitressin is the name given by Burroughs Wellcome to the vasopressin preparations* which they manufacture e g Pitressin Tannate in oil

With this method the highest specific gravity obtained should be 1·020 or above. The effect of vasopressin tannate in oil only lasts about 24–48 hours so that the test can be repeated at fairly frequent intervals, both to confirm earlier results and to follow the course of a disease. Intervals of one week between tests have been found satisfactory.

The use of vasopressin tannate in oil has one serious disadvantage. The vasopressin tannate is mixed with oil and after prolonged standing it settles at the bottom of the ampoule where it looks like an insignificant brown discoloration and is easily overlooked. To avoid its being left behind, those actually giving the injection should be aware of this fact, and that it is thus often necessary to warm and shake the ampoule vigorously before use, and occasionally to scrape the sediment with the point of a needle. The transfer of the oil and vasopressin from the ampoule to the syringe is also made easier by using a large-bore needle.

Interpretation of the Urine Concentration Test

In order to understand the result of a concentration test it is necessary to keep in mind the three factors which are directly concerned in concentrating the urine; they are:

1. The concentration of circulating antidiuretic hormone (ADH).
2. The ability of the tubules to respond to the antidiuretic hormone.
3. The rate of solute output.

The concentration of circulating ADH is regulated by both the amount of ADH produced by the neurohypophysis and the rate at which it is being destroyed at the periphery, particularly in the liver and kidney. As yet there is no evidence of any pathological condition in which there is an abnormal rate of ADH destruction; changes in the circulating level of ADH are therefore due to alterations in its production by the neurohypophysis. A wide variety of factors influences neurohypophyseal function including the osmolality of the extracellular fluid, the blood volume and certain disease processes involving the hypothalamus or the posterior pituitary.

The ability of the tubules to respond to ADH depends on the integrity of the loop of Henle, the collecting tubule and the flow of blood through the vasa recta. The response may be impaired because of a congenital defect or an acquired disturbance; the latter may be reversible. The acquired disturbances which may be reversible initially include fever, urinary tract obstruction (Fig 5 11), potassium deficiency, hypercalcuria, water intoxication, hypoadrenalism, and occasionally certain acute phases of some generalised allergic diseases In many of these conditions the urine may be persistently hypotonic even during dehydration or the intravenous administration of vasopressin, this is particularly characteristic of hypercalcæmia and potassium deficiency Chronic pyelonephritis is also occasionally responsible for a state of fixed hypotonicity

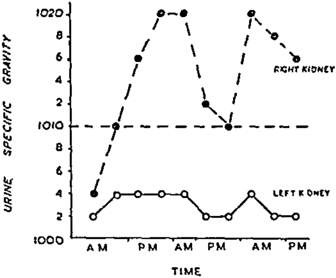

Fig 5 11 *The effect of a raised intrapelvic pressure on the ability to concentrate* The observations were made on a patient with a left sided hydronephrosis due to a recent obstruction of the left ureter The urine from the left kidney was obtained through a nephrostomy tube and from the right kidney in the usual way The hydronephrotic kidney continually *excreted a strongly hypotonic urine though the high concentrations of the* urine from the right kidney indicated that there were adequate concentrations of antidiuretic substances in the circulating blood

The Rate of Solute Output If a person is dehydrated for a considerable time so that the level of circulating ADH, and the concentration of the urine are high, and if at this time some substance is then administered which is promptly excreted by the kidney, there is not only a prompt increase in solute output, but also a rise in urine flow and *a decrease in urine concentration* This phenomenon is called an osmotic diuresis and is illustrated by the curve A in Fig 5 12 It can be seen that in these conditions of maximal ADH activity an osmotic diuresis is associated with a fall in urine concentration towards that of plasma, but that the urine concentration remains greater than plasma

If on another occasion an osmotic diuresis is induced when the level of circulating ADH is less than during the experiment just described, similar changes in urine flow and concentration will take place, but the curve will be at a lower level; i.e. line B in Fig. 5.12. The lower the concentration of circulating ADH therefore, the lower the curve until, when there is no ADH in the circulation, an osmotic diuresis increases the urine flow but there is little or no associated change in the urine concentration, for it is already at its lowest (line C).

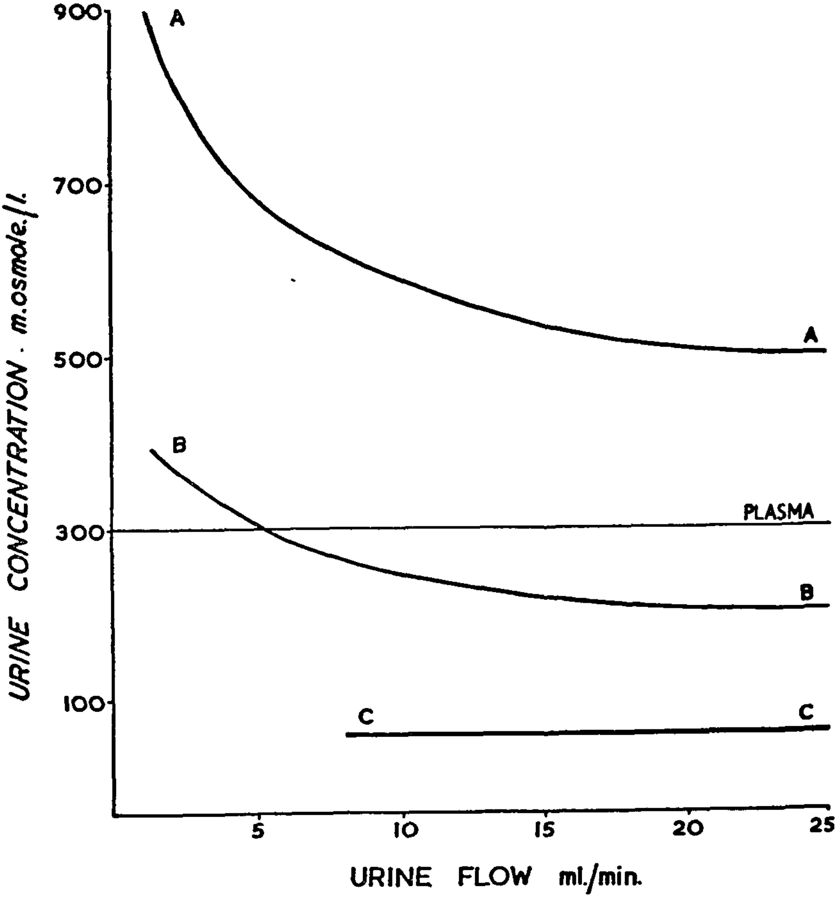

Fig. 5.12. Osmotic diuresis in the normal kidney; A was obtained in a normal subject during severe dehydration; B in a patient with diabetes insipidus during the infusion of minimal quantities of vasopressin and C in the same patient when no vasopressin was being given.

The increased rate of urine flow and fall in urine concentration during maximal ADH activity (line A) are mainly due to a fall in the osmolality of the interstitial fluid in the medulla. This is probably due to (i) an increased rate of flow through the loop of Henle which disturbs the counter-current system (p 42), and (ii) the increased delivery of fluid to the collecting tubule which causes large quantities of water to be transferred into the medullary interstitial space Lines B and C, however, are principally due to the increased delivery of hypotonic fluid from the loops of Henle into distal and collecting ducts the permeability of which is only partly altered, or unaltered by ADH. It is evident that a high solute excretion rate is not compatible with a high urine concentration however great the level of circulating ADH The most important clinical example of an osmotic diuresis is that associated with the glycosuria of diabetes

If the total solute output remains unchanged but the number of nephrons is reduced, the solute excretion rate for the remaining nephrons is increased and an osmotic diuresis occurs in each nephron This is the situation that can be produced experimentally in animals by excising one kidney completely and about 50 per cent of the other Though *the remaining piece of kidney contains presumably normal* nephrons such an animal is unable to produce concentrated urine It is likely that similar conditions exist in many forms of renal disease associated with much parenchymatous destruction If the patient is eating normally the total solute excretion rate must remain relatively unchanged, yet these solutes are being excreted through a considerably reduced number of nephrons. In such circumstances a diminished capacity to concentrate is probably due in part to the osmotic diuresis *per nephron* which must be taking place, rather than any particular *inability of the tubules to respond to circulating ADH*

Procedure to Test the Tubule's Ability to Produce a Dilute Urine and Eliminate a Water Load

The test is started early in the morning and is performed in the fasting state After emptying the bladder the patient is asked to drink water (20 ml per Kg body weight) in about 10–20 minutes It is inadvisable to ask the patient to drink this amount more rapidly, for in some cases this will induce nausea and vomiting with the release of large quantities of ADH, it is also advisable to sweeten the water with fruit juice Urine is collected at hourly intervals for four hours and the concentration of each specimen and the cumulative total are measured During these four hours a normal person should excrete 75 per cent or more of the amount ingested, and the concentration of at least one specimen should be below S G 1 004

Apart from the risks of nausea and vomiting this test is subject to other causes of inaccuracy For instance, smoking may inhibit a *water diuresis, or emotional reactions* may cause either (i) an exuberantly high rate of urine flow unrelated to the patient's normal

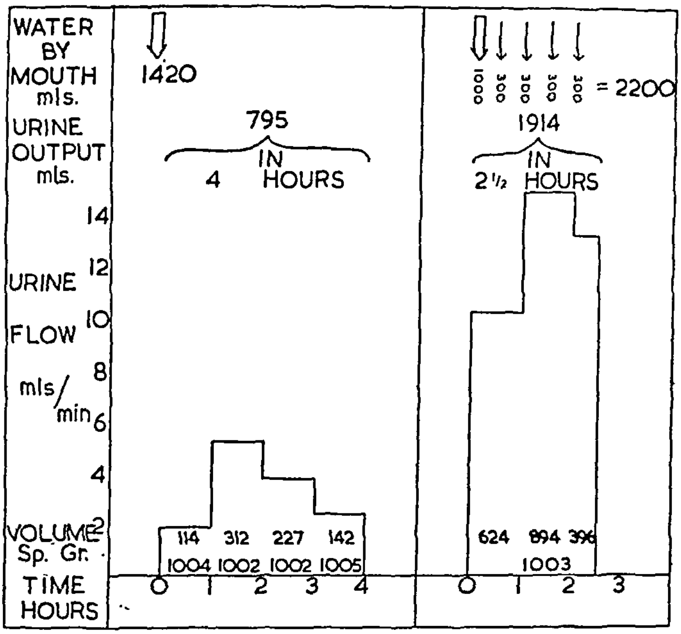

FIG. 5.13. The effect of a water load in an emotional subject. On the first occasion only 50 per cent of the amount ingested was excreted in the subsequent four hours, but the next time nearly 100 per cent was passed in only two and a half hours.

response to a water load; or (ii) an almost complete inhibition of the expected diuresis; an example of both of these is illustrated in Fig. 5.13.

In addition to renal disease a persistent impairment in the ability to excrete a water load can be caused by many other disturbances including hydroadrenalism, or an inverted diurnal rhythm.

CONTROL OF ACID-BASE BALANCE AND URINE ACIDITY

Plasma hydrogen-ion concentration is maintained close to *p*H 7·4 by a variety of mechanisms. The most important are the buffering capacity of the cells and the skeleton, and the control of the $B.HCO_3/H.HCO_3$ buffer system in the plasma (where B = metallic cations, i.e. sodium, potassium and calcium). In this system the level of carbonic acid is regulated by the excretion of CO_2 by the lungs, and the concentration of bicarbonate (mainly in the form of sodium bicarbonate) by the kidney's ability to excrete an acid or alkaline urine and to generate bicarbonate.

On a normal diet and with a normal ventilation the *p*H of the blood can only remain constant if about 40–60 mEq. of hydrogen ions are excreted in the urine each day. This represents the net load which remains to be disposed of, when metabolism is normal. The kidney's ability to excrete hydrogen ions depends on the tubule's capacity to secrete both hydrogen and ammonia ions into the tubular fluid In the urine the hydrogen ions are either (i) free, or potentially free in association with a buffer or (ii) combined with ammonia in the form of *ammonium*

The amount of alkali that must be added to acid urine to return the *p*H to that of plasma is a measure of the net quantity of free and potentially free hydrogen ions in the urine and is known as the titratable acid The sum of the urinary titratable acidity and ammonium is a measure of the kidney s excretion of hydrogen ions i e its contribution towards preventing the internal environment from becoming acid

Tubular Control of Hydrogen Ion Secretion and Bicarbonate Reabsorption

The secretion of hydrogen ions into the tubular fluid not only permits the excretion of free hydrogen ions but is also necessary for the reabsorption of sodium bicarbonate and it is responsible for generating fresh bicarbonate

Hydrogen ion secretion from the tubule cell and bicarbonate reabsorption from the tubule lumen occur in both the proximal and distal tubule and are dependent on the intracellular production of free hydrogen ions Throughout the nephron this is probably due primarily to the formation of carbonic acid from the hydration of carbon dioxide Some of the carbonic acid then dissociates into hydrogen and bicarbonate ions i e

$$CO_2 + H_2O \overset{\substack{\text{Carbonic}\\ \text{anhydrase}}}{\rightleftharpoons} H_2CO_3 \rightleftharpoons H^+ \; HCO_3$$

These additional hydrogen ions are available for transfer into the tubular fluid in exchange for the sodium ions which are being actively transported from the tubule lumen into the cell The positively charged hydrogen ions diffuse into the tubule lumen not only because of their higher intracellular concentration (consequent upon their continuous intracellular production) but also because of the electrical gradient caused by the simultaneous transfer of the negatively charged sodium ions from the tubule lumen

Most of the hydrogen ions which enter the tubular fluid combine with bicarbonate to form carbonic acid which then either diffuses back into the cell (Fig 5 14) or is dehydrated in the tubule lumen to carbon dioxide and water when the carbon dioxide then diffuses back into the cell (Fig 5 15) Once in the cell the carbonic acid or carbon dioxide are then reutilised or diffuse into the blood The hydrogen ions which remain in the tubule fluid are finally excreted in the urine either as free ions or in association with a buffer particularly phosphate (Fig 5 16) or they are combined with ammonia. The transfer of hydrogen ions from the tubule cell into the tubule fluid in the distal tubule can continue in the face of a steep rise in the concentration of hydrogen ions in the tubular fluid; the highest concentration which can be sustained is about *p*H 4·3. At this point the further transfer of hydrogen ions depends on the supply of buffer or ammonia.

It is probable that the sodium ions which have entered the proximal tubule cells diffuse from the cell into the peri-tubular venous blood, whereas those that have entered distal tubule cells are actively secreted from the cell into the blood.

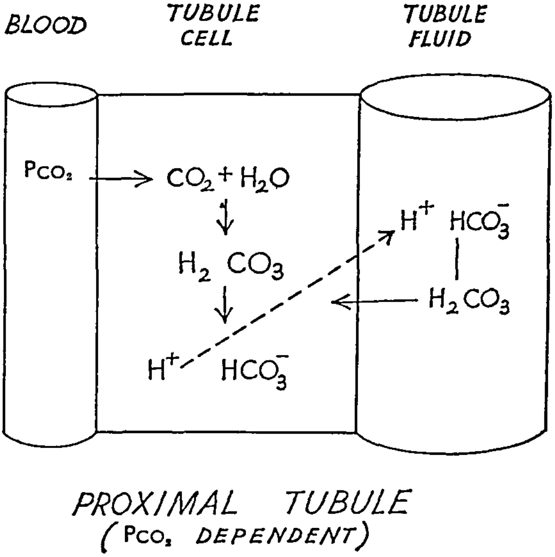

FIG. 5.14 Reabsorption of bicarbonate in proximal tubule.

The intracellular formation and concentration of hydrogen ions in the tubule cells and their secretion into the tubule lumen is dependent on a variety of factors. In the proximal tubule it appears to be dependent on the ambient carbon dioxide tension (Fig. 5.14), whereas in the distal tubule it is independent of the carbon dioxide tension but related to the intracellular content of carbonic anhydrase which accelerates the hydration of carbon dioxide (Fig. 5.15). In addition, in the distal tubule, sodium reabsorption from the lumen of the tubule into the cell can cause potassium ions to flow from the cell into the tubule lumen as well as, or instead of, hydrogen ions. The relative intracellular concentration of these two ions probably determines in what proportions they are excreted in the urine. For instance, the increase in intracellular potassium concentration which is produced by the administration of potassium chloride diminishes distal tubular secretion of hydrogen ions and increases the urinary excretion of potassium As a result less bicarbonate is reabsorbed, therefore more is excreted and there is a fall in plasma bicarbonate Alternatively, if the cellular production of hydrogen ions in the distal tubule is inhibited by the administration of a carbonic anhydrase inhibitor such as acetazoleamide (Diamox) the reabsorption of sodium in the distal tubule will again be associated with a rise in potassium excretion and a diminution of hydrogen ion excretion On this occasion, however, the increased potassium excretion is due to a decrease of intracellular hydrogen ion concentration and not to an increase in potassium concentration

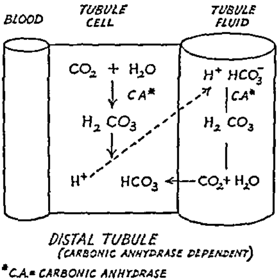

Fig 5 15 Reabsorption of bicarbonate in distal tubule

Bicarbonate reabsorption, like that of phosphate and sodium reabsorption, is closely related to glomerular filtration rate In other words, changes in glomerular filtration of bicarbonate are accompanied by almost equal change in tubular reabsorption of bicarbonate with the result that the change in filtration produces little if any change in bicarbonate excretion It is probable that the mechanism responsible for this automatic adjustment is related to a change in the size of the tubule (p 70) It is important that this phenomenon be remembered when studying the effect of various stimuli on tubular reabsorption if such stimuli also produce changes in glomerular filtration rate It is for this reason that in such studies changes in bicarbonate (and phosphate) reabsorption are related to a constant glomerular filtration (Figs 5 18 and 5 24)

Other Mechanisms Involved in the Control of Bicarbonate Excretion

It is clear from the above that one of the main factors which influences bicarbonate excretion is the secretion of hydrogen ions into the tubule lumen. When a sufficient quantity is secreted into the tubule lumen all the filtered bicarbonate can be reabsorbed—if less hydrogen ions are secreted some of the filtered bicarbonate will not be reabsorbed and will therefore be excreted. It has also been pointed out that two of the factors which influence this tubular secretion of hydrogen ions are variations in Pco_2 and body stores of potassium. The secretion of hydrogen ions and therefore the reabsorption and excretion of bicarbonate are also influenced by:

1. Variations in the secretion of adrenal cortical hormones.
2. Variations in plasma calcium concentration.
3. Variations in plasma chloride concentration.

In addition bicarbonate reabsorption is also determined by:

4. The integrity of the counter-current system in the medulla.

Insufficiency of adrenal cortical hormones leads to a metabolic acidosis and an excess to a metabolic alkalosis. The mechanisms are not clear. Perhaps a diminution or an excessive sodium reabsorption has a parallel effect on the secretion of hydrogen ions. Hypercalcæmia probably causes a rise in urinary hydrogen ion excretion by stimulating carbonic anhydrase activity.

Plasma chloride concentration affects the secretion of hydrogen ions and therefore bicarbonate excretion in the following way: Let us assume that the plasma chloride concentration is low but that of plasma sodium is normal, and that the tubule attempts to reabsorb nearly all the sodium in the normal way. It has been pointed out earlier that the reabsorption of the positively charged sodium ions from the tubule lumen causes a rise in the electrical potential difference between the cell and the lumen of the tubule; the cell tending to become increasingly positive and the lumen increasingly negative. This potential gradient causes the negatively charged chloride ions to diffuse from the tubule lumen into the cell and the positively charged hydrogen ions to diffuse from the cell into the lumen. If the supply of chloride ions to the tubule lumen falls because of a fall in plasma chloride and if at the same time sodium reabsorption remains normal, it is clear that even if all the chloride ions diffuse back into the tubule cell, the steepness of the potential gradient will remain higher than when the supply of chloride is normal. It is then inevitable that the passive flux of hydrogen ions from the tubule cell into the tubule lumen will increase and thus enhance bicarbonate reabsorption.

The Pco_2 of an alkaline urine excreted by a normal person may be around 100 mm Hg The kidney's ability to excrete a urine with such a high Pco_2 is due to counter-current systems in the medulla which trap the carbon dioxide (p 42) This phenomenon permits the simultaneous presence in the urine of very high concentrations of bicarbonate and thus increases the kidney s capacity to excrete large amounts of bicarbonate

Procedure Used to Detect the Presence of an Abnormal Handling of Bicarbonate by the Kidneys

This is done by estimating the tubules maximal capacity to reabsorb bicarbonate (*Tm HCO_3 see p 79) The patient should not be taking* diuretics and should be emotionally at rest to avoid hyperventilation *An intravenous infusion of sodium bicarbonate is given so as to raise the* plasma bicarbonate to approximately 28–30 mEq /l As bicarbonate reabsorption is related to glomerular filtration the maximal rate of bicarbonate reabsorption is then adjusted to a standard quantity of glomerular filtrate, it is usual to adjust to one litre of filtrate

The normal maximal rate of bicarbonate reabsorption is 26 to 29 mEq /l of glomerular filtrate It is reduced in renal failure, certain selective tubular disturbances and in some patients with essential hypertension without overt evidence of other renal functional abnormalities, it is also lowered when hyperventilation lowers Pco_2, on the other hand, it is raised in respiratory failure with a raised Pco_2 in vomiting with hydrochloric acid loss, in potassium deficiency and hyperadrenalism

The plasma bicarbonate tends to be low when the ability to reabsorb bicarbonate is reduced and raised when the ability to reabsorb bicarbonate is raised

Acidosis

In chronic respiratory acidosis (e g emphysema) the rise in Pco_2 causes an increase in the concentration of hydrogen ions both in the plasma and the cells, including the tubule cells This in turn increases the tubular secretion of *hydrogen ions from the cells into the* tubule lumen and thus causes a rise in both the urinary excretion of *hydrogen ions and an increased intracellular generation of bicarbonate* The increased secretion of hydrogen ions into the tubule lumen ensures that all the filtered bicarbonate is reabsorbed, in addition, however, some of the extra bicarbonate generated in the tubule cell also diffuses into the blood The combination of total bicarbonate reabsorption, intracellular bicarbonate generation with diffusion into the plasma, and increased urinary hydrogen ion excretion causes a rise in plasma bicarbonate. The ability to reabsorb all the filtered bicarbonate increases in parallel with the rise in Pco_2 and remains complete with Pco_2 tensions of 80 mm.Hg. and above. The generation of extra bicarbonate and urinary excretion of hydrogen ions, however, are only sufficient to compensate for a rise of Pco_2 up to 60 mm.Hg. This can be seen in Fig. 5.17 where up to a rise in Pco_2 of 60 mm.Hg. the accompanying rise in bicarbonate is sufficient to prevent a major change in plasma *p*H.

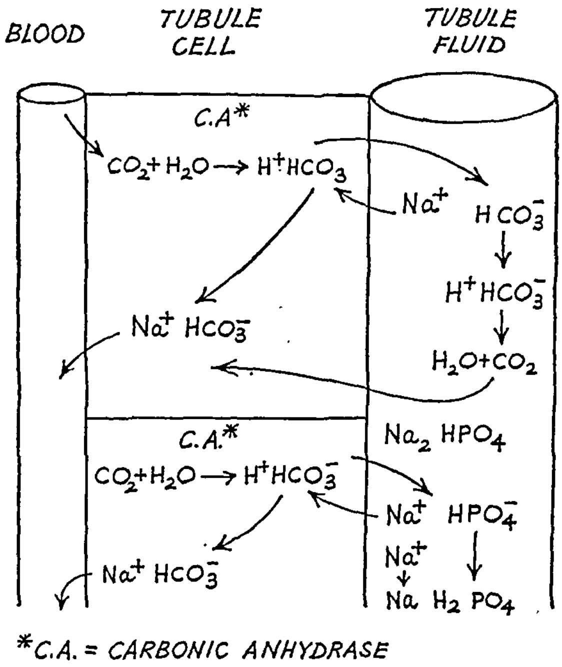

FIG. 5.16 Secretion of hydrogen ions in the distal tubule, and bicarbonate reabsorption and generation. Note that the excretion of titratable acid is chiefly in the form of acid phosphate, and that the formation of this salt is accompanied by the generation of fresh bicarbonate ions.

Above a Pco_2 of 60 mm.Hg. the urine remains free of bicarbonate but the rise in plasma bicarbonate is minimal and there is a sharp fall in plasma *p*H. The inadequacy of the urinary hydrogen ion excretion is particularly striking and is due to an impaired production of ammonia. It is probable that this impairment is due directly to the poisonous effect of the rise in Pco_2 on the tubule cell's capacity to form ammonia. In metabolic acidosis the ammonia production is much higher. The sustained rise in bicarbonate reabsorption is necessarily associated with a sustained diminution in chloride reabsorption. It results in a severe chloride loss and a low plasma chloride.

In a metabolic acidosis (e g diabetic ketosis or ammonium chloride *administration) there is also an increased concentration of hydrogen* ions in the plasma but because of the accompanying hyperventilation the carbon dioxide tension is *reduced* Nevertheless the tubules again increase the secretion of hydrogen ions and the reabsorption of bicarbonate It appears therefore that in a metabolic acidosis the inhibitory effect of the reduced carbon dioxide tension on the intracellular production of hydrogen ions is swamped by the persistent rise in extracellular fluid hydrogen ion concentration In normal man when

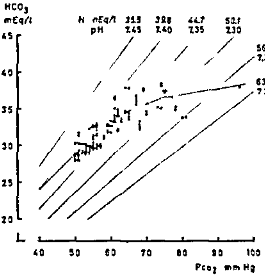

Fig 5 17 The relation of arterial P_{CO_2} pH and bicarbonate in 20 patients with pulmonary insufficiency breathing air (Refsum 1964 Clin. Sci.)

the plasma bicarbonate concentration falls below 25 mEq /l the urinary excretion of bicarbonate rapidly diminishes (Fig 5 16) In the metabolic acidosis associated with renal disease however this compensatory mechanism may break down and in some patients bicarbonate excretion *may continue down to plasma bicarbonate levels of about 20 mEq /l* The maximum acidity which the tubule can sustain is approximately pH 4 6 which limits the kidney s ability to excrete large quantities of free hydrogen ions unless the urinary content of phosphate buffer is raised or there are large volumes of urine as in diabetic ketosis

The kidney s capacity to deal with a metabolic acidosis is entirely dependent on tubular function i e the tubule s ability to excrete hydrogen ions and ammonia

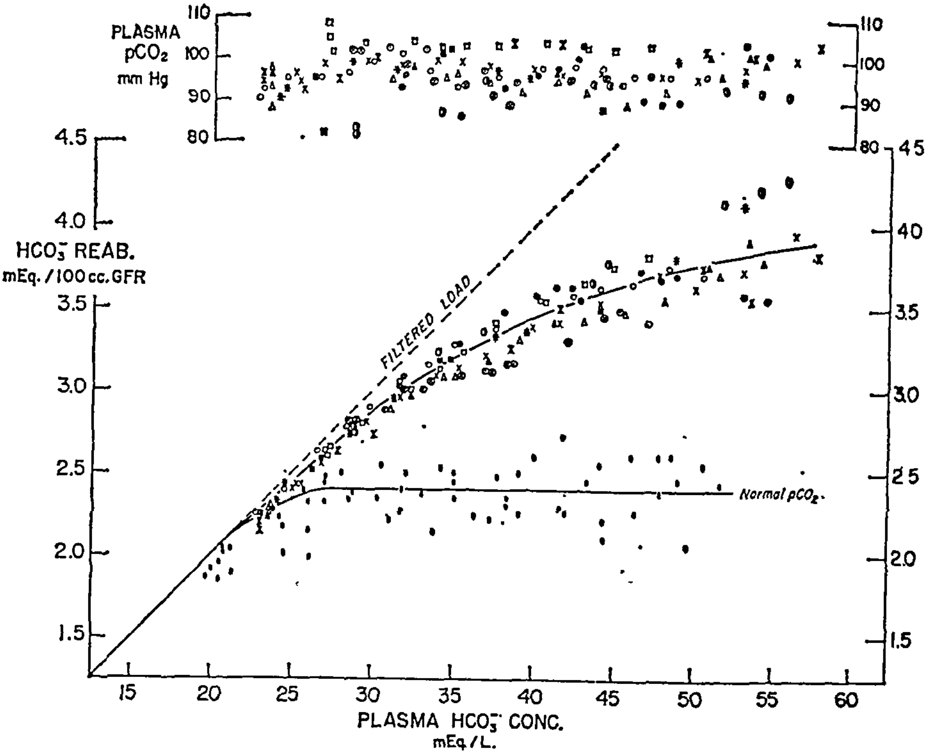

FIG. 5.18. Bicarbonate reabsorption in the dog. The effect of acute increases in Pco_2 during the progressive elevation of plasma bicarbonate by the intravenous infusion of $NaHCO_3$. The lower line = values obtained at normal Pco_2 between 35 and 45 mm.Hg. The upper curved line = values obtained when the Pco_2 was between 80 and 110 mm.Hg. It can be seen that the bicarbonate reabsorption is greater when the Pco_2 is raised. It is clear that at both concentrations of Pco_2 the capacity to reabsorb bicarbonate flattens out, but at different values, each of which is called a bicarbonate Tm. (Schwartz, Falbriard and Lemieux, 1959, *J. clin. Invest.*)

Alkalosis

When there is a respiratory alkalosis (e.g. voluntary hyperventilation, left heart failure, or excessive artificial ventilation as in severe poliomyelitis) there is a fall both in the plasma hydrogen ion concentration and the carbon dioxide tension. Both these factors will decrease the availability of the hydrogen ions in the tubule cell so that less hydrogen ions are excreted and bicarbonate reabsorption is decreased; the plasma will therefore tend to become less alkaline. In an acute respiratory alkalosis a simultaneous increase in the excretion of sodium and potassium can also be demonstrated.

In a metabolic alkalosis (e.g. sodium bicarbonate administration) there is also a fall in hydrogen ion concentration but, because of the accompanying hypoventilation, there is a *rise* in the carbon dioxide tension. The rise in carbon dioxide tension does cause a slight increase in bicarbonate reabsorption but, when the plasma bicarbonate concentration rises above 27 mEq./l., bicarbonate reabsorption does not increase further and urinary excretion of bicarbonate then equals the increasing quantities which are filtered; if the glomerular filtration rate is normal this spill over prevents the concentration of plasma bicarbonate from rising steeply. In contrast to metabolic acidosis therefore, which is controlled entirely by tubular mechanisms, the ability of the kidneys to control a metabolic alkalosis is mainly related to the glomerlar filtration rate. But tubular function is also involved for very large quantities of bicarbonate can only be excreted if the countercurrent system in the medulla is sufficiently intact to maintain a high P_{CO_2} (p. 42).

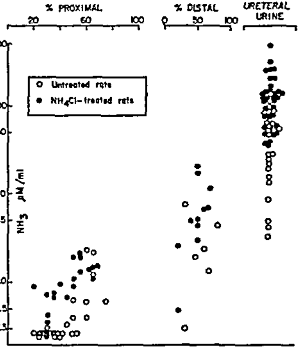

Fig. 5.10 Site of ammonia production in the rat nephron (Glabman, Klose and Giebisch, 1963 *Amer. J. Physiol.*)

Ammonia Excretion

Ammonia (NH_3) is formed in the tubule cells throughout the whole length of the nephron, with the exception of the thin part of the loop of Henle (Fig. 5.10). Ammonia is a base with no electrical charge which is highly soluble in lipids, for this reason it diffuses easily across cell membranes. When ammonia combines with a hydrogen ion, however, and becomes ammonium (NH_4^+) it is charged, has a low lipid solubility and only diffuses across cell membranes with some difficulty. The ammonia formed within the tubule cells diffuses passively from the cells into the tubular lumen on the one side of the cell and the peritubular venous capillaries on the other. When the ammonia in the tubule fluid combines with a hydrogen ion and forms an ammonium ion it is trapped within the lumen and most of it remains there to be excreted in the urine. The formation of ammonium in the tubule lumen diminishes the intraluminal concentration of ammonia so that the diffusion of ammonia from the cell to the tubule lumen down a concentration gradient continues. On the other hand, if the secretion of hydrogen ions from the cell into the tubule lumen is diminished the formation of ammonium will be less and the intraluminal concentration of ammonia will rise; this in turn will reduce the rate of diffusion of ammonia from the cell to the lumen.

Ammonia is formed within tubule cells mainly from the action of glutaminase on glutamine, though other amino acids are also involved. This process is depressed by accummulation of intracellular ammonia and accelerated when the concentration falls; conversely, it is accelerated in potassium deficiency, perhaps because of the intracellular acidosis that then occurs which probably reduces the concentration of free ammonia. It is important to remember that free ammonia diffuses both into the tubule lumen and into the peritubular venous capillaries and that the amount that diffuses into the blood is therefore inversely proportional to that which is secreted into the urine. Clinically this is particularly relevant in patients with liver failure who develop oliguria or anuria.

Urinary ammonium excreted is inversely related to the *p*H of the urine and almost ceases when the urine becomes alkaline (Fig. 5.20). The increase in ammonium excretion, which occurs as the urine *p*H falls, is due in part to the increased formation of ammonia in the tubule cell mentioned above and due to the depletion of intracellular ammonia. But if the urine continues to be acid the amount of ammonium excreted continues to rise after the *p*H has reached its minimum; this may be due to an increasing concentration of glutaminase in the tubule cells.

In normal circumstances the daily excretion of ammonium and free hydrogen ions is approximately the same (i.e. 20–30 mEq. of each). When there is a need for an increased excretion of both (as in diabetic ketosis) the increase in ammonium greatly exceeds that of free hydrogen ions. Ammonium excretion may reach 400 mEq./day whereas the simultaneous excretion of free hydrogen ions will only be 70–100 mEq./day. These are very high excretion rates and are rarely seen except in prolonged diabetic ketosis The response of a normal person to large quantities of ammonium chloride is illustrated in Fig 5 20 It can be seen that after a delay of five days the ammonium excretion is about three times greater than that of free hydrogen ions

Procedure Used to Estimate the Tubule's Ability to Excrete an Acid Urine and to Excrete Hydrogen Ions and Ammonia

The tubule's capacity to excrete hydrogen ions and ammonia is estimated by measuring its response to the oral administration of ammonium chloride The ammonium chloride molecule is metabolised to urea and HCl The addition of these hydrogen ions into the extracellular fluid tends to make it acidotic, and in order to compensate for this tendency the kidney excretes increased quantities of hydrogen ions both as titratable acid and as ammonium and the urine becomes more acid If the patient is severely acidotic the administration of ammonium chloride is unnecessary Ammonium chloride is given either as a single dose in the morning, the urine being studied within the next

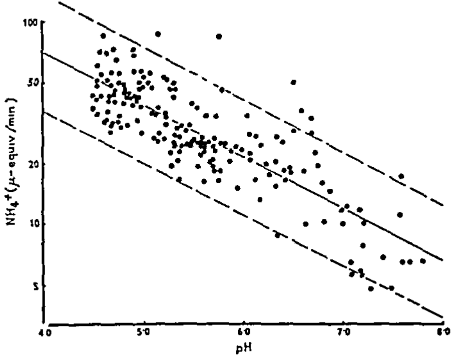

Fig 5 20 Relation between the excretion of ammonium and urinary *p*H in normal subjects a few hours after the oral ingestion of a single dose of ammonium chloride (short test) The calculated regression line and 95 per cent range of observations are shown (Wrong and Davies 1959 *Quart J Med*) eight hours; or it is adminstered in divided doses each day for five days when each daily collection of urine is studied, particularly that obtained on the fifth day.

The Short Test. After two control collections of urine of about 1–2 hours duration the patient is given 0·1 g. (1·9 mEq.) of ammonium chloride per kg. body weight orally at about 10 a.m.; in a patient of average size this is about 7 g. In order to avoid gastric irritation this amount is given over an hour, in gelatin capsules of 0·5 to 1·0 g. together with a litre of water (enteric coated tablets are not used for they often appear intact in the stools). Venous blood is taken before and 2–4 hours after the administration of ammonium chloride. The urine may be collected at hourly intervals, but as the changes are maximal and relatively constant after the fifth hour a single urine collection taken between 3 and 5 p.m. will usually suffice. The urine *p*H should fall below 5·3, and hydrogen ion excretion (i.e. combined titratable acidity and ammonium) should rise above 60 μEq./min.; the titratable acid excretion should be greater than 25 μEq./min. and ammonium excretion greater than 35 μEq./min.

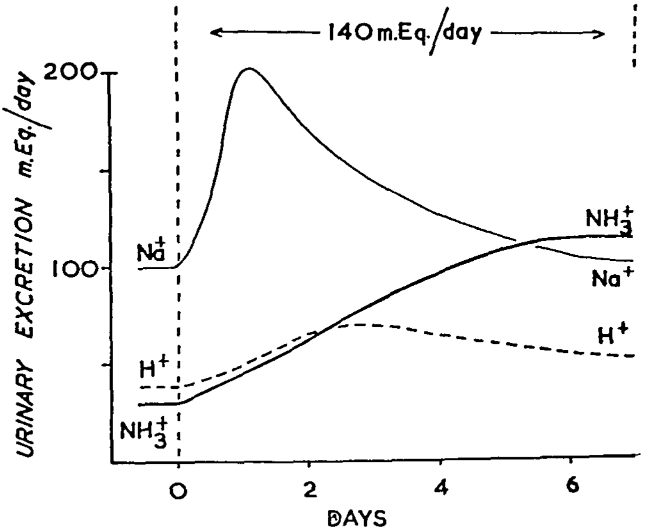

FIG. 5.21. The effect of 140 mEq./day of ammonium chloride by mouth on the urinary excretion of sodium, hydrogen and ammonium in a normal subject.

The Long Test. Following two to three days control observations 7·5 g. (140 mEq.) of ammonium chloride is given by mouth in divided doses each day for five days. The maximum titratable acidity is reached in three to four days, whereas ammonium excretion takes four to five days to reach its peak. The chloride ions of the ammonium chloride are also eliminated through the kidney; at first these are excreted with almost equal quantities of sodium, but after two to three days the *initial increase in sodium excretion subsides (Fig 5 21) At the end* of four to five days the urine *p*H should have fallen below 5 0 and the *daily combined excretion of ammonium and titratable acid should* rise above control values by about 120 mEq /day If the renal response *is normal, plasma bicarbonate and chloride concentrations should not* alter by more than 6 mEq /l

The ability to reduce the pH of the urine is always impaired in renal tubular acidosis (p 216) and potassium deficiency (p 198), it is sometimes impaired in hypercalcuria, while it appears superficially normal in the chronic renal failure which accompanies loss of nephrons (p 168) The ability to excrete titratable acid normally is depressed in renal tubular acidosis, potassium deficiency, hypercalcuria and chronic renal failure As ammonium excretion is related to the *p*H of the urine the value obtained in these tests must be considered in relation to the *p*H of the urine The normal relationship is illustrated in Fig 5 20 It can only be claimed that the capacity to excrete ammonium is depressed if it is lower than a normal person s capabilities at the same urine *p*H According to these criteria ammonia excretion is depressed in chronic renal failure and in some cases of hypercalcuria, it is normal in most cases of renal tubular acidosis and some cases of potassium deficiency, and it is raised in most cases of potassium deficiency and some cases of renal tubular acidosis

SODIUM EXCRETION

Sodium is the principal solid constituent of the extracellular fluid, the volume and osmolality of which are closely related to the amount of sodium it contains In man, except for acute changes, there is overwhelming evidence that sodium excretion is unrelated to the rate of glomerular filtration, for patients with chronic renal failure keep in sodium equilibrium though they have extremely low glomerular filtration rates Variations in sodium excretion are therefore related to changes in tubular reabsorption It is generally considered that approximately 80 per cent of the sodium that is filtered is reabsorbed *together with chloride and bicarbonate in the proximal tubule*

There is now good evidence that the sodium ion is actively reabsorbed This mechanism is closely related to the tubular secretion of hydrogen ions and potassium, particularly in the distal tubule and collecting tubule For instance, under conditions of *intense sodium* reabsorption the administration of sodium sulphate causes a precipitate fall in urine *p*H and a rise in titratable acid *excretion, together with a* rise in potassium excretion This is due to the negatively charged sodium ions being actively reabsorbed from the tubular lumen while the positively charged sulphate ions remain behind owing to their poor penetrative qualities. The electrical gradient which results is then responsible for a passive movement of hydrogen and potassium ions from the tubule cells into the tubule lumen. Such an intravenous infusion of sodium sulphate during sodium deprivation is a highly abnormal situation, but the urinary changes which it induces probably reflects the normal pattern of events, i.e. an active reabsorption of sodium from the tubule lumen into the tubule cell sets up a potential gradient along which chloride ions travel into the cell while hydrogen and potassium ions move in the opposite direction from the cell into the tubule fluid.

The biochemical mechanisms involved in sodium reabsorption are largely unknown but they appear to be related to those of calcium reabsorption. In acute experiments the excretion of these two ions nearly always changes in the same direction.

Some of the known factors which influence the tubular reabsorption of sodium include the action of various known hormones, the arterial pressure, an osmotic diuresis, the diameter of the tubule lumen, and the renal nerves. It is very probable also that other, as yet unidentified, hormones also play an important part, particularly in relation to blood volume changes.

The steroids, progesterone, testosterone, cortisone and especially aldosterone, increase tubular reabsorption of sodium, so do adrenaline and noradrenaline; at the moment the action of angiotensin is ill-defined but it probably also causes an increase in sodium reabsorption. The presence of cortisone is necessary for the changes in sodium excretion which take place as a result of acute changes in blood volume (see below); but cortisone itself is not the substance which is directly responsible for the alterations in tubular function which occur. This phenomenon which is sometimes called the "permissive" action of cortisone is not confined to tubular function.

In an acute experiment where an isolated kidney in a warm saline bath is being perfused by blood from an intact animal, a sudden change in the perfusion pressure to that kidney will produce a parallel change in its sodium excretion. Alternatively, if the perfusion pressure is kept constant and the animal perfusing the kidney is given an infusion of saline the increase in sodium excretion from the perfused kidney is directly proportional to the perfusion pressure. In other words, with a constant perfusion pressure of 100 mm.Hg. the rise in sodium excretion is minimal, whereas when it is 200 mm.Hg. the rise in sodium excretion is very large (Fig. 5.22). A similar pattern occurs in patients with a high blood pressure in whom an intravenous infusion of saline produces a much greater rise in sodium excretion than when it is given to a person with a normal blood pressure. The mechanisms involved in this phenomenon are not clear: *they are not related to changes in glomerular* filtration rate. It is possible that they are in part due to changes in *tubular diameter (see below) caused by changes in peritubular capillary* pressure.

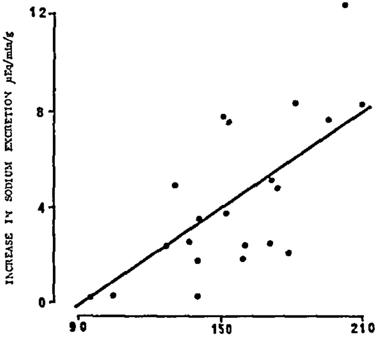

FIG. 5.22 The rise in sodium excretion which occurs in an isolated kidney during the administration of a standard infusion of saline to the animal perfusing the kidney. The rise in sodium excretion is greater at the higher perfusion pressures (McDonald and de Wardener)

An osmotic diuresis is always associated with an increase in sodium excretion. This can sometimes be of great clinical importance, e.g. in diabetes.

The two most interesting recent advances in trying to understand those mechanisms which control sodium reabsorption have been the revelation that, in general, the diameter of the tubule is directly related *to sodium reabsorption, and that an acute expansion of the blood* volume probably inhibits sodium reabsorption by a change in the con*centration of some circulating substance other than a salt retaining* steroid. Teleologically the first is admirable and it explains the repetitious finding that acute changes in *glomerular filtration* have little if any effect on sodium excretion. It is probable that a sudden rise in glomerular filtration rate causes a sudden increase in the diameter of the proximal tubule and that this distension causes an immediate increase in sodium reabsorption (Fig. 5.23), and vice versa. Alternatively, changes in tubular diameter can be produced by changes in peritubular venous capillary pressure. It is not understood how a change in tubular diameter affects sodium reabsorption. Nevertheless, it is probable that the effective mechanism is closely related to the transtubular pressure gradient across the tubule wall rather than the actual diameter of the tubule.

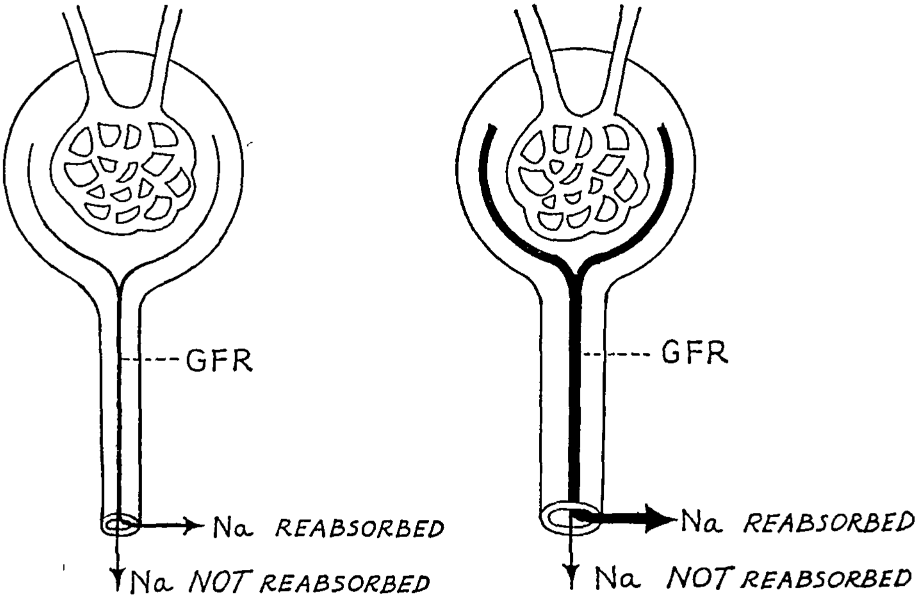

FIG. 5.23 Effect on sodium excretion and reabsorption in the proximal tubule of an increase in tubular diameter caused by a sudden rise in glomerular filtration rate. Although there is an increase in the amount of sodium that is filtered when the glomerular filtration rate rises, the amount of sodium reabsorbed by the proximal tubule also rises and the amount of sodium which emerges from the proximal tubule is unchanged. (Diagram based on findings of Rector, Brunner and Seldin 1966, *J. clin. Invest.* and Gertz, 1966, *Pflug. Arch. Ges. Physiol.*)

Prolonged changes in blood volume influence the secretion of aldosterone and thus sodium excretion by a mechanism which is discussed in section 110. Acute changes in blood volume, however, influence sodium reabsorption by some hormonal mechanism other than that of changing the concentration of circulating aldosterone. The nature of this other hormone is not known; there is a suggestion that it may come from the brain.

In acute experiments the renal nerves can be shown to influence sodium excretion Nevertheless, patients who rely on transplanted kidneys for survival are in sodium balance, it is unlikely therefore that renal nerves play an important part in the control of sodium metabolism

Procedure Used to Test the Tubules Ability to Control Sodium Excretion

The efficiency of the tubules' ability to control sodium excretion can be tested either by increasing or decreasing the intake of sodium An excess of sodium, however, is rarely given, for an inability to excrete a sodium load is more frequently due to extrarenal influences stimulating the tubules to retain sodium (i e cardiac failure, liver failure, etc) *than to renal disease itself The dangers which follow an inability to* excrete a sodium load may also be more sudden in onset, dangerous, and difficult to treat than those which may accompany sodium deficiency

Reducing the intake of sodium is a more specific test of intrinsic tubular abnormality The patient is placed on a normal ward diet containing about 100 mEq of sodium per day, and the daily urinary sodium excretion is estimated for a control period during which it should (in the absence of diarrhœa or much sweating) be approximately 15 mEq /day less than the intake (to allow for loss in sweat and fæces) The dietary intake of salt is then reduced to about 10 mEq /day, which is the content of the average hospital " salt-free " diet Within 7–10 days urinary sodium excretion should *also be down to 10 mEq* per day

The kidney's response to a low salt diet depends not only on tubular function but also *on the many mechanisms* which influence the tubule to retain salt A more direct test of tubular ability to control salt excretion is obtained by keeping the patient on a normal diet and giving 2 mg of 9 α-fluorohydrocortisone twice a day for two or three days when the urinary excretion of sodium should fall below 10 mEq /day.

Apart from Addison's disease and severe glycosuria, an inability to conserve sodium is seen occasionally in chronic renal failure, particularly *with chronic pyelonephritis (p 109), it also occurs sometimes during* the diuretic phase of acute renal failure, and very rarely as a result of a primary disturbance of tubular function (Renal Tubular Acidosis, p 216) In contrast, in chronic renal failure there may sometimes be an impaired ability to excrete a high intake of sodium

CHLORIDE EXCRETION

It has already been pointed out (p 68) that the activity of the sodium pump in transporting sodium ions out of the lumen of the tubule causes an electrical potential gradient between the cell and the lumen; the lumen being negatively charged and the cell positively. It is probable that this is sufficient to account for the reabsorption of chloride from the tubule lumen which accompanies sodium reabsorption, the chloride ion diffusing passively down the potential gradient from the lumen into the tubule cell. Under exceptional experimental conditions, however, it can be shown that active processes for the reabsorption of chloride also exist. The importance of these active mechanisms in the differential absorption of chloride ions, as opposed to bicarbonate ions, which occurs in those conditions where there is a reciprocal change in the plasma concentration of these two ions, is not known.

POTASSIUM EXCRETION

Potassium is the principal intracellular cation. It should be remembered that in this respect the cells of the tubule are the same as other cells.

It has been shown both by direct tubular puncture and by indirect experiments, that the potassium that is filtered at the glomerulus is probably all reabsorbed in the proximal tubule, and that the amount which eventually appears in the urine is actively secreted by the distal tubule. As with sodium, therefore, glomerular filtration rate is unrelated to potassium excretion; a point of the greatest importance to patients suffering from most forms of chronic renal disease and in whom glomerular filtration rate is severely impaired.

There is evidence that some of the mechanisms responsible for potassium secretion are also related to the distal tubular reabsorption of sodium and secretion of hydrogen ions (see above). When sodium is reabsorbed from the distal tubular lumen it is exchanged for hydrogen or potassium ions secreted from the tubule cell. The rates of secretion of these two ions are influenced by many factors and have an inverse relationship. One of these factors is the relative concentration of each ion in the tubule cell, i.e. when the supply of intracellular hydrogen ions increases or the concentration of potassium ions diminishes, potassium secretion decreases. Another is the amount of sodium reaching the distal tubule for reabsorption. For instance, in chronic renal failure sodium and potassium " leaks " may occur together. It is possible that this is due to an impaired sodium reabsorption in the proximal tubule so that more sodium goes into the distal tubule. The increased reabsorption of sodium in the distal tubule which then takes place causes an excessive amount of potassium to be transferred from the cell into the tubular fluid.

Many abnormal conditions are accompanied by a temporary increase in potassium excretion Sometimes it occurs in relation to a rise in plasma potassium caused by a shift of potassium from the intracellular to the extracellular space

Procedure Used to Test the Tubules Ability to Control Potassium Excretion

Unlike sodium where the serum concentration tends to remain *unchanged or fall with sodium retention serum potassium rises with* potassium retention This makes the testing of the kidney s ability to deal with an increased potassium load a potentially dangerous procedure and it is therefore never attempted Urinary excretion is the main route of potassium elimination and if the serum potassium is found to be persistently raised it is clear that there is a tubular defect of potassium excretion

To show that there is a potassium deficit and that it is due to excess urinary loss is more difficult Except when serum potassium is below 3 mEq /l a low concentration is uncertain evidence of potassium deficiency, *though it is more likely if there is a concomitant rise in* serum bicarbonate (p 58) If potassium depletion is suspected or evident and there is no obvious diminished intake or leak from the intestinal tract it is almost certain that it is due to abnormal loss in the urine This is confirmed by measuring the oral intake of potassium and its output in the urine

The patient is placed on a normal diet containing 80-100 mEq of potassium per day and the daily urinary potassium excretion is *measured for a control period during which it should be 10-20 mEq less than the intake (this amount is eliminated in the faeces)* If the urinary excretion is greater than the intake particularly when the plasma potassium concentration is low there is unequivocal evidence of a urinary leak of potassium The following relationship between the lower concentrations of plasma potassium and the urinary excretion of potassium when the patient is eating a normal ward diet is a reliable substitute for a balance study When there is a renal leak of potassium and the plasma concentration of potassium has *fallen to 3 mEq /l or lower the urinary excretion of potassium* is greater than 20 mEq / 24 hours whereas if the potassium deficiency is due to some other cause (such as diarrhoea) the urinary excretion of potassium at these low plasma potassium concentrations will be less than 20 mEq /24 hours This distinction will usually persist even when potassium deficiency has caused severe renal functional impairment After some years however the potassium deficiency itself affects the kidney s ability to retain potassium

If the findings on a normal diet are within normal limits and yet a urinary leak of potassium seems very likely the patient is placed on a low potassium diet, since in some instances the tubular abnormality may only become apparent when the potassium intake is reduced. On a diet containing 25–30 mEq./day of potassium the urinary excretion of potassium should fall to 25–30 mEq./day within four to seven days.

An excessive urinary loss of potassium can be caused by renal tubular acidosis, aldosteronism, Cushing's disease, and the prolonged administration of steroids or certain diuretics (e.g. chlorothiazide). It is probable that it is rarely, if ever, due to an acquired renal disease.

CALCIUM EXCRETION

Calcium reabsorption from the glomerular filtrate normally occurs in the proximal tubule. When the serum calcium rises, however, and there is an increased amount of calcium filtered, evidence of calcium reabsorption can also be obtained in the distal and collecting tubules. The initial functional disturbances associated with hypercalcuria are an impairment in the ability to concentrate and to acidify the urine.

Urinary calcium excretion rises and falls with the concentration of filtrable plasma calcium and to a minor extent with changes in glomerular filtration rate. Parathyroid hormone *decreases* calcium clearance, increases calcium absorption from the bowel, and liberates calcium from bone; these mechanisms tend to raise the plasma calcium, but the net effect is an increase in calcium excretion. It is doubtful if a high urinary excretion of calcium is ever due to a primary disturbance of tubular function. It is usually due either to a raised plasma calcium or increased parathormone activity such as a parathyroid tumour, when the hypercalcuria may itself cause severe renal structural and functional disturbances (p. 203). Occasionally if there is a severe depression of glomerular filtration rate hypercalcæmia may not be associated with hypercalcuria; hypercalcuria may then only appear if renal failure improves.

Procedure Used to Determine the Presence of Hypercalcuria

Hypercalcuria is difficult to define. A few years ago there were reports that 90 per cent of normal subjects studied in England excreted less than 300 mg. of calcium per day. It was therefore considered that a urinary excretion of more than 300 mg. per day was greater than normal. Recently, however, there have been claims that the proportion of normal subjects who excrete more than 300 mg. per day is rising; perhaps as a result of the Milk Marketing Board's advertising. In 1967 therefore the upper limit of normal calcium excretion is probably nearer 400 mg./day for men and 300 mg./day for women.

More precisely hypercalcuria can be defined as the daily excretion of more than 200 mg of calcium when the diet contains less than 150 mg A simple way to perform such a balance study is to place the patient on a rice diet The rice is cooked in distilled water,* but salt can be added in normal amounts and jams, sugar and fruit are allowed drinking water must also be distilled Such a diet contains about 90–130 mg of calcium a day The urine calcium excretion is estimated on the fourth day when it should contain less than 200 mg

MAGNESIUM EXCRETION

The average daily intake of magnesium is approximately 250 mg with a urinary excretion of 100 mg per day The filtration of magnesium at the glomerulus and its reabsorption from the tubule parallel that of calcium In the same way the control of urinary magnesium excretion appears to be almost identical to that of calcium in that it is raised by a rise in the concentration of circulating parathormone etc It is probable that calcium and magnesium share a common intratubular transport mechanism Nevertheless magnesium metabolism is less disturbed than calcium metabolism in renal disease Paradoxically in acute renal failure, though the urinary excretion of both calcium and magnesium cease there is a fall in plasma calcium and a rise in plasma magnesium In chronic renal failure plasma magnesium remains normal even when the glomerular filtration rate falls below 5 ml /min Very rarely a renal lesion may cause an excessive loss of magnesium and cause magnesium deficiency

Procedure Used to Detect a Renal Leak of Magnesium

There is no standardised way to do this Nevertheless it is usually not difficult to establish that a renal leak of magnesium is taking place for with rare exceptions it only occurs in patients with advanced renal disease If such a patient has a low plasma magnesium and there is no other obvious cause for magnesium deficiency then it is overwhelmingly likely that the deficiency is due to excess urinary excretion This can be confirmed by finding that though the plasma magnesium is low the urinary excretion of magnesium is not reduced

PHOSPHATE EXCRETION

There is no evidence that phosphate is secreted by the tubule Phosphate excretion therefore depends on a balance between filtration and reabsorption In normal circumstances all the phosphate in the plasma is filtrable. Tubular reabsorption is mainly controlled by the concentrations of circulating parathormone, calcitonin and thyroid hormone. Phosphate reabsorption (like bicarbonate and sodium reabsorption) is also related to glomerular filtration rate (p. 70), in such a way that changes in filtration rate produce little change in phosphate excretion. On the other hand, changes in plasma phosphate concentration produce changes in phosphate clearance, i.e. a rise in plasma phosphate is associated with an increased phosphate clearance. This is immensely important for the diurnal swing of plasma phosphate is very pronounced and is maximal in the morning; a time which is often chosen to do studies on renal function.

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* London tap water contains 10 mg /100 ml of calcium.

Procedure Used to Detect the Presence of an Abnormal Handling of Phosphate by the Kidney

The only reliable and reproducible method is to estimate the maximal capacity of the tubules to reabsorb phosphate (Tm PO_4, p. 79). This is achieved by raising the plasma phosphate concentration by a steady intravenous infusion of buffered phosphate to a plasma

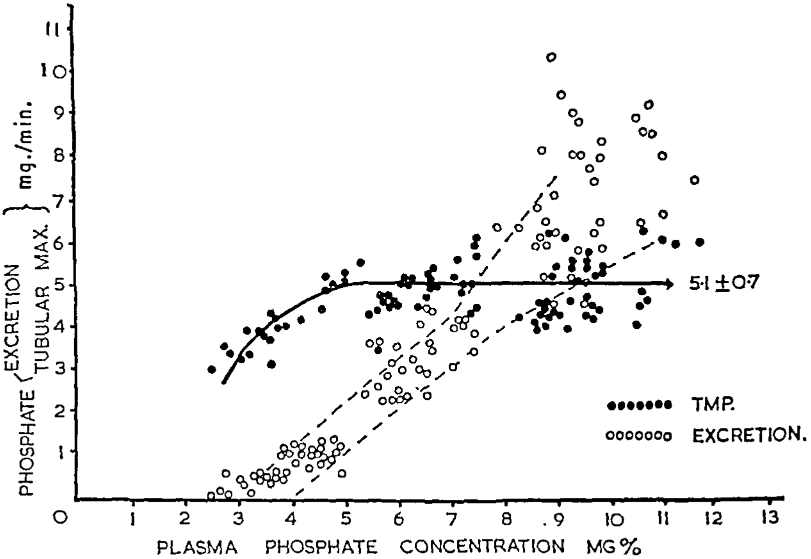

FIG. 5.24 Single estimation of $TmPO_4$ and phosphate excretion corrected for filtration rate, plotted against phosphate concentrations in normal subjects ("phosphate tubular max" = phosphate reabsorbed; compare this with bicarbonate reabsorption on p. 62). Phosphate reabsorption reaches a maximum of about 5.0 mg./min. and then levels out. The value at which it does so is the $TmPO_4$, or maximum capacity of the tubule to reabsorb phosphate. In this figure the reabsorption and excretion have been adjusted to a glomerular filtration rate of 131 ml/min.; it is now more usual to relate these to 1 l. of filtrate (see text). (Anderson & Parsons, 1963, *Clin. Sci.*)

level greater than 5 mg /100 ml Conditions both before and during this test have to be rigorously controlled, a high phosphate diet before the test must be avoided, because of the diurnal rhythm of phosphate the test should always be done at the same time of day, as glucose is absorbed along the same pathways as phosphate the patient should be fasting, other substances such as PAH which may compete for tubular transport mechanisms should be avoided, and the test should not be prolonged for otherwise it may induce endocrine changes which will alter the result And when all these precautions have been taken the normal range is still so wide that it may not be exceeded even in proven primary hyperparathyroidism Fig 5 24 shows the results in normal subjects The maximal capacity to reabsorb phosphate (Tm PO_4)

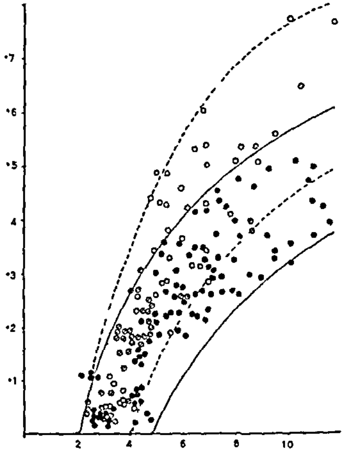

Fig 5 25 Relation between serum inorganic phosphate (abscissæ mg /100 ml) and the ratio of renal clearance of phosphate to glomerular filtration rate (ordinates) McGeown and Bull 1957 *Brit med Bull*) is 38 ± 5 mg./l. of glomerular filtrate. Parathormone diminishes phosphate reabsorption while thyroid hormone increases it. It is also reduced in severe renal failure and certain primary disturbances of the tubules. When the capacity to reabsorb is diminished the plasma phosphate will fall, and it will rise when reabsorption is increased.

Other methods used include estimates of the clearance of phosphate alone or the phosphate to creatinine clearance ratio. The first is valueless and the second is only of value if the duration of the clearance period is 24 hours, the dietary intake of phosphate is constant from day to day and the plasma phosphate sample is always taken 4–5 hours after the last meal (e.g. at midday). As the phosphate to creatinine clearance ratio rises as the plasma phosphate concentration increases the results obtained must therefore be compared with those obtained over a wide range of plasma phosphate concentrations in normal subjects (Fig. 5.25).

AMINO ACID EXCRETION

Amino acids are filtered, and actively reabsorbed in the proximal tubule by four main transport mechanisms, each of which deals with one of the following groups of amino acids:

1. The monoamino-monocarboxylic amino acids such as alamine, valine, trytophan and cysteine.
2. The dibasic amino acids: lysine, arginine, ornithine and cystine.
3. The dicarboxylic amino acids: glutamic and aspartic acids.
4. The imino-acid and glycine group: proline, hydroxyproline and glycine.

Amino-aciduria or excessive excretion of amino acids is classified into " overflow " or " renal " types. Overflow amino-aciduria is due to disorders of metabolism in which the circulating concentration of certain amino acids rises. The amount of these amino acids which is then filtered exceeds the tubules' capacity for reabsorption and the quantity which is not reabosrbed " overflows " into the urine. The inability to deaminate amino acids in severe liver failure causes an overflow of all groups of amino acids while phenylketonuria which is due to an impaired ability to metabolise phenylanaline is an example of a single amino acid overflow amino-aciduria.

In renal amino-aciduria the primary defect is either an absence or deficiency or either group 1 or 2 active transport mechanisms. This can arise either as a hereditary anomaly of amino acid transport without other evidence of abnormal tubular function e.g. cystinuria and disease; or as one of several tubular abnormalities all of them caused by damage to the proximal tubules. Such damage may develop acutely as in cadmium and uranium poisoning or more chronically with copper in Wilson's disease, or galactose in infantile galactosæmia

URIC ACID EXCRETION

Normally, only about 10 per cent of the uric acid that passes through the glomerulus is excreted in the urine, i e about 90 per cent appears to be reabsorbed There is some evidence, however, that nearly 100 per cent of the filtered uric acid is reabsorbed in the proximal tubule *and that the uric acid that is excreted in the urine has been secreted by the distal tubule* The daily *excretion of uric acid is 0 5 to 1 0 g* The amount depends to a large extent on the content of cell nuclei in the diet, for uric acid is derived from purine bases liberated in the degradation of both ingested, and endogenous nucleoproteins

The concentrations of uric acid found in the urine are such that the uric acid is in a supersaturated state The liability to precipitation is obviously greatest when the urine is acid The solubility of total uric acid i e free uric acid and urates in urine is only 8 mg /100 ml at *pH* 5 0, 22 mg /100 ml at *pH* 6 0, and 158 mg /100 ml at *pH* 7 0 *In addition precipitation* of sodium urate in the urine and in the medulla *is probably enhanced by the high concentrations of sodium in the* medulla and urine when concentrated urine is being formed

There are many conditions in which there is a selective impairment in the ability to excrete uric acid Some of them are due to a raised concentration of plasma lactic acid which is a well established inhibitor of uric acid excretion In renal failure the ability to excrete uric acid remains normal until the glomerular filtration rate falls below 20 ml /min (p 358)

MAXIMAL CAPACITY OF THE TUBULES TO TRANSPORT GLUCOSE AND PARA-AMINO HIPPURIC ACID

The capacity of the tubules to reabsorb or secrete certain substances is limited, and a measure of this is obtained by estimating the maximal amount that the tubules can either secrete or reabsorb in one minute This amount is referred to as the Tm of that substance (derived from the words tubule and maximal "), it has a certain value particularly in relation to bicarbonate (p 62) and phosphate (p 76) excretion

Reabsorption Tm

The *Tm of glucose* (Tm_g) is a good example of a reabsorptive Tm When blood glucose is within normal limits it is unusual for there to be glucose in the urine, since all the filtered glucose has been reabsorbed. To determine Tm_g an intravenous infusion of glucose is given at a rate sufficient to raise the blood glucose substantially. Glycosuria occurs and the amount of glucose reabsorbed is calculated as follows:

glucose filtered — glucose excreted = glucose reabsorbed

or

$$GFR \times P_g - U_g \times V = T_g,$$

where GFR is glomerular filtration rate per minute, P_g is plasma glucose concentration, U_g the urine glucose concentration, V the rate of urine flow, and T_g the rate of glucose reabsorbed as mg. per minute. The rate of glucose administration continues to be increased in a stepwise manner and the measurements are repeated; blood glucose and glycosuria increase steadily, but there comes a point beyond which the quantity of glucose reabsorbed remains constant; this is the Tm_g, and in normal man is 323 ± 64 mg./min.

The plasma glucose concentration at which glucose first appears in the urine is sometimes referred to as the renal threshold for glucose. This level is roughly correlated with Tm_g but is a less constant value, for it is influenced by alterations in glomerular filtration rate. At the renal threshold for glucose the quantity of glucose being presented to the tubules by the glomerular filtrate is only just sufficient to exceed the tubule's ability to reabsorb all the glucose passing through; if plasma glucose remains unchanged but there is a fall in filtration rate, no glucose will appear in the urine and the renal threshold will have altered. But when estimating Tm_g the blood glucose concentration is raised to such high values that, so long as a nephron has some filtration, the amount of glucose being presented to the tubule for reabsorption is far in excess of its maximum reabsorbing capacity; in this way alterations in glomerular filtration rate cannot influence the amount reabsorbed.

The main value of a Tm_g is that it gives a quantitative expression of the total mass of functioning tubular cells. It is rarely estimated.

The Tm of bicarbonate and phosphate reabsorption is of more interest and has been discussed earlier (pp. 62 & 76). With these ions however, the term is more elastic, for though at any one moment a Tm can be demonstrated it can be altered by various manœuvres. For instance, Tm_{HCO_3} can be increased by raising Pco_2, and Tm_{PO_4} can be lowered by giving parathormone. In addition, unlike Tm_g which is uninfluenced by changes in glomerular filtration, tubular reabsorption of bicarbonate and phosphate varies directly with changes in glomerular filtration rate, so that for purposes of comparison Tm_{HCO_3} and Tm_{PO_4} have to be related to a standard glomerular filtration rate (p. 70).

INTERPRETATION OF THE RESULTS OF THE TWO MOST WIDELY USED TESTS OF RENAL FUNCTION, i.e. GLOMERULAR FILTRATION RATE AND THE ABILITY TO CONCENTRATE

The information derived from these two tests alone allows a certain measure of subdivision of renal disorders

Glomerular Function (Filtration rate)	*Tubular Function (Ability to concentrate)*	*Interpretation*	*Renal Disorder*
Decreased	Decreased.	Number of functioning nephrons diminished.	Chronic glomerular nephritis, polycystic kidneys, etc, etc
		or Both glomerular and tubular function impaired, number of functioning nephrons variable	1 Severe urinary obstruction. 2 Severe renal ischæmia, e g. acute renal *failure* from loss of blood 3 Severe electrolyte abnormality, e g potassium deficiency *and hypercalcæmia*. 4. Renal poisons e g acute renal failure from the ingestion of mercury.
Normal or slightly decreased.	Decreased.	Tubular function definitely impaired, glomerular function normal or impaired to a much smaller extent than tubular function	1 Urinary tract obstruction, either recent, *moderate or* unilateral 2 Chronic pyelonephritis in its early stages. 3 Moderate electrolyte *abnormality*, e g potassium deficiency and hypercalcæmia 4 Inborn functional defect of renal *tubules*, *e g*. Fanconi s syndrome 5 Compulsive polydipsia
Decreased.	Normal	Glomerular function impaired, tubular function normal	1. Moderate acute renal ischæmia, e g hæmorrhage insufficient to cause *acute renal failure*. 2 Acute nephritis

Secretion Tm

In this context a substance is considered to be secreted by the tubules only if the amount excreted in the urine is greater than that which has been filtered. This is, of course, a convenient but grossly arbitrary definition, for some substances which are actively secreted by the tubules (e.g. potassium) have a total urinary excretion which is usually less than that which has been filtered. To measure the true amount secreted, therefore, it would be necessary to know the amount which has been reabsorbed, and in ordinary circumstances this is not possible.

Those substances which have the greatest rate of tubular secretion according to the definition given above are those which are not normally present in body fluids, and include diodone, phenol red, penicillin and para-amino-hippuric acid (PAH). Because of its ease of estimation and its high rate of active secretion PAH is the substance which has been most often used to obtain a secretory Tm. The procedure is similar to that used for estimating glucose Tm. Intravenous PAH is administered at a rate sufficient to maintain plasma PAH level at about 20 mg. per 100 ml. at which level the tubules are being presented with PAH at a rate much greater than their ability to secrete it into the tubule lumen; $\mathrm{Tm}_{\mathrm{PAH}}$ is then calculated as follows:

$$\text{PAH excreted} - \text{PAH filtered} = \text{PAH actively secreted,}$$

or

$$U_{\mathrm{PAH}} \times V - \mathrm{GFR} \times P_{\mathrm{PAH}} = \mathrm{Tm}_{\mathrm{PAH}}.$$

In normal man $\mathrm{Tm}_{\mathrm{PAH}}$ is 68 ± 11 mg./min. Again, it is rarely estimated.

Limitations of Existing Renal Function Tests

There is as yet no test which will give information about the number of functioning nephrons. This is a serious disadvantage. The kidney's capacity to hypertrophy is very great and it has been repeatedly shown that the removal of one kidney produces little or no permanent change in overall function. Similarly there is much histological evidence that in those chronic renal diseases in which nephrons are destroyed, the surviving nephrons hypertrophy, and it must be assumed that the function of the surviving nephrons increase with their size. It is therefore theoretically possible for a renal disease to destroy about half the nephron population and yet produce little or no change in renal function, and it follows that an unchanging renal function is not proof that a disease is quiescent, e.g. in persistent pyelonephritis. Conversely, when renal function is persistently reduced to half its normal value it is almost certain that a great deal more than half of the original renal parenchyma must have been destroyed These speculations would be unnecessary if, during life it were possible to obtain an estimate of the number of surviving nephrons

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6

DIURNAL RHYTHM

THE urinary excretion of water and most electrolytes is normally greater during the day than at night, a fortunate phenomenon which ensures that the night's repose shall be undisturbed This pattern is not only due to the fact that fluid and food are taken during the day it will persist even if identical quantities of food and water are ingested at regular intervals throughout the 24 hours As the evening approaches and during the night, the excretion of sodium potassium bicarbonate and chloride ions gradually diminishes while the *p*H of the urine falls, and its concentration rises, the process is reversed in the morning (Fig 6 1)

The mechanism responsible for this rhythm is unknown, it has been shown that there is a small nocturnal fall in glomerular filtration rate, but this cannot explain all the changes that occur for instance, the excretion of phosphate *increases* at night and diminishes during the day It is possible that the changes in water excretion and particularly the changes in urine concentration, follow a diurnal alteration in antidiuretic hormone secretion There is no doubt that an antidiuretic mechanism is present, for at night a large drink of water only produces a small increase in urine flow The changes in electrolyte excretion are preceded, by a few hours, by similar fluctuations in steroid excretion It is probable that this is only coincidental, for it fails to explain why the changes in sodium and potassium excretion should be parallel, it has also been reported that under certain conditions the excretion of steroid will rise gradually throughout the day and night, and yet the diurnal rhythm of electrolyte and water excretion continues uninterruptedly

A normal diurnal rhythm persists during undernutrition, water deprivation, salt deprivation, the sustained action of pitressin and a temporary disturbance of sleep rhythm For instance, a person going from east to west on a ship across the Atlantic will show a peak of electrolyte excretion one hour (ship time) earlier each day But the clock "gains" an hour each day so that in fact the diurnal rhythm remains unchanged in relation to European time Reversal or abolition of the diurnal rhythm occurs commonly in the four most frequent causes of generalised oedema, i e cardiac failure, liver failure, the nephrotic

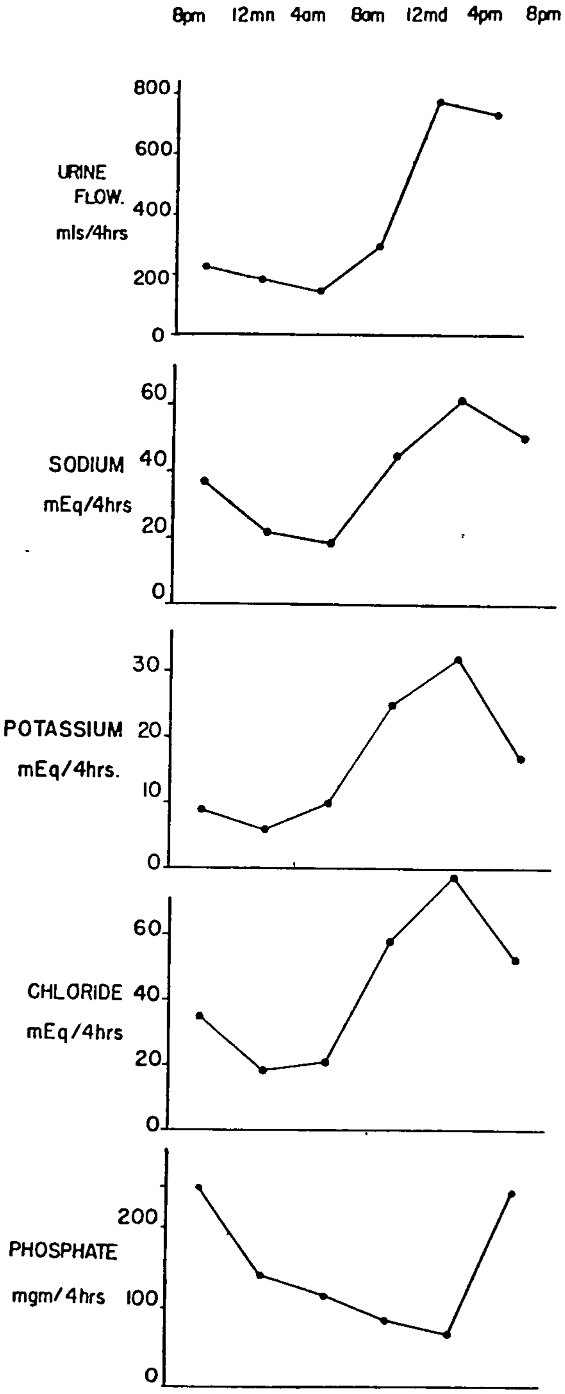

FIG. 6.1. Diurnal rhythm of urinary excretion of water, sodium, potassium, chloride and phosphate in a normal subject.

syndrome and malnutrition In these conditions the volume of urine passed at night may be equal to or exceed the daytime total (Fig 6 2) It may also be reversed in chronic renal failure, small bowel insufficiency (e g idiopathic steatorrhœa) Addison's disease, and following a head injury In a normal person the diurnal rhythm can be abolished and occasionally reversed by the administration of cortisone

A knowledge of a patient's pattern of electrolyte and water excretion may sometimes be of help in treatment An œdematous person with a reversed rhythm, for instance, may only have a diuresis following the administration of a diuretic, if it is given in the evening rather than in the morning

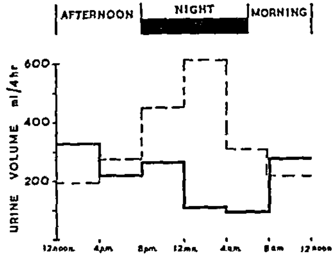

Fig 6 2 Pathological reversal of the diurnal rhythm of urinary excretion of water (----) compared with the normal rhythm (——)

The diurnal rhythms of urinary constituents are often accompanied by *diurnal rhythms in their plasma concentrations,* though synchronous changes in blood and urine are not necessarily in the same direction This is of the utmost importance when trying to assess changes in renal function Inattention to these rhythms was the cause of much of the confusion which surrounded earlier discussions on phosphate excretion

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7

RENAL FUNCTION IN RELATION TO AGE

Renal Function in the Fœtus

The outstanding fact is that fœtal urine is hypotonic to its own plasma

Renal Function in Infancy

In contrast to adults the intake of food and the rate of growth are more important than the kidney in keeping the biochemical environment of the infant stable In addition, though the infant s kidney is perfectly adequate for normal purposes it is less adaptable than that of an adult in an emergency

Glomerular filtration rate calculated on a surface area basis, is proportionately less than in an adult and yet the concentration of urea in the blood is lower This is due to the relatively larger quantities of nitrogen that are being retained at this time of life, and in normal circumstances the lower glomerular filtration rate is perfectly adequate to dispose of the small amount of waste products of protein catabolism The hazards of this situation are evident when the child becomes ill and ceases to store nitrogen A sharp increase in protein catabolism is then liable to produce a rapid rise in blood urea and if protein administration is continued the blood urea may rise rapidly though there has been no alteration in the glomerular filtration rate

Tubular Function The ability to dilute and concentrate the urine to adult levels does not take place until approximately the fourteenth day and the third month respectively The ability to excrete a water load does not reach adult proportions until the end of the first month The inability to concentrate the urine is due initially to (i) an inability to secrete antidiuretic hormone (ADH), (ii) an inability to respond to ADH because the renal medulla has not developed sufficiently, and (iii) the small amounts of urea passing down the tubule After a few weeks the ability to secrete ADH appears and the kidney has matured sufficiently to enable it to respond to ADH but the ability to concentrate remains low At this point, however, if an infant is given suitable quantities of urea by mouth the ability to concentrate rises to adult levels within a few hours, the increase in osmolality being equal to the increased concentration of urea in the urine

The control of sodium excretion is even less elastic than that of water and an excess infusion of normal saline may produce a hypertonic œdema because of the greater difficulty in getting rid of sodium. Alternatively, urinary sodium excretion may continue though there is a negative balance of sodium from diarrhœa or vomiting. Consequently, during the first few months an inadequate intake of water or an attack of diarrhœa may lead to severe dehydration; or an excessive administration of water may cause overhydration.

The other tubular functions which have been found to be relatively less efficient than in an adult are the ability to excrete a highly acid urine, and both $\mathrm{Tm}_{\mathrm{PAH}}$ and Tm_g (p. 79). All functions become comparable to those of an adult by the end of the first year. Ammonia excretion, however, is within normal limits in the first few days.

Titratable acid excretion is remarkably low for the first year of life. This is due in part to a poor ability to secrete hydrogen ions against a gradient and also to the low phosphate content of the urine. The low urinary phosphate content is due to the infant's retention of phosphate for the formation of bone and muscle. If phosphate is administered titratable acid excretion rises and the usually low plasma bicarbonate values rise to adult levels. It appears therefore that the infant's normal state is one of metabolic acidosis secondary to a combination of inadequate kidneys and insufficient urinary buffer. This explains the infant's liability to develop severe acidosis if given large quantities of dietary protein.

Proteinuria and glycosuria occur in about a quarter of normal premature infants, and infants up to the third day, when the urine than becomes free of protein and glucose.

Renal Function During Senescence

After the age of 30 there is a gradual reduction in renal functional capacity. The functions which have been studied include glomerular filtration, renal blood flow and secretion Tm, urea clearance, and the ability to concentrate.

By the age of 90 each of these functions has decreased to approximately half its value at the age of 30. Histological appearances show that there is a gradual loss of nephrons so that it is highly probable that every function is involved. It is certainly very noticeable that elderly patients are not able to concentrate their urine to the same extent as adolescents.

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8

THE RENAL CIRCULATION

At rest about one-fifth of the cardiac output flows through the kidney, the normal renal blood flow being approximately 1,100 ml./min. It is a greater irrigation per unit weight of tissue than any other organ. This extraordinary phenomenon is confined to the cortex; the medulla only receives 6 per cent of the total renal blood flow and has an irrigation which is comparable to that of other tissues. The reason for this high cortical perfusion is not understood for, though a substantial and sustained reduction in renal blood flow is always associated with some fall in glomerular filtration rate, renal function in all other measurable respects may remain perfectly normal. In the following discussion it is to be remembered that changes in renal blood flow are generally accompanied by similar changes in the glomerular filtration rate, though frequently the degree of change may be different.

SOME FACTORS WHICH CAUSE A REDUCTION IN RENAL BLOOD FLOW

The normal renal blood flow is very great, consequently if a change does occur, the flow is nearly always reduced. The upright posture, undernutrition, exercise, pain, heat, adrenaline and advancing years are some of the physiological factors associated with such a reduction. The pathological causes are discussed below.

Circulatory Insufficiency

Clinically the most frequent cause of a fall in renal blood flow is circulatory insufficiency. Contraction of the blood volume and cardiac failure both cause renal vasoconstriction and a fall in renal blood flow, whether or not there is a concomitant decrease in blood pressure.

Contraction of the blood volume may be secondary to traumatic, surgical or spontaneous bleeding, acute hæmolysis, severe diarrhœa and vomiting, barbiturate poisoning, burns, or negative protein balance. Sudden changes in blood volume produce the most marked changes in the renal circulation, but there is a delay between the time of the hæmorrhage and the onset of renal vasoconstriction. A hæmorrhage which is severe enough to induce peripheral vasoconstriction, with pallor and coldness of the hands feet and face may not cause a fall in renal blood flow within the next one to two hours If however, the blood volume remains reduced for four to seven hours there is severe *renal vasoconstriction which may be sufficient to cause necrosis of the* renal cortex The cause of this vasoconstriction is nervous and humoral and this may be the reason why the constriction takes a few hours to become maximal Therapeutically the delay is sometimes an advantage *for early transfusion may prevent the onset of severe renal ischæmia* but conversely once ischæmia has developed transfusion is only associated with a slow recovery the ischæmia continuing for several hours though the blood volume is normal

Cardiac failure induces renal vasoconstriction both when the cardiac output is low (when the fall in renal blood flow is proportionately greater than the fall in cardiac output) and when the output is high as in cor pulmonale and thyrotoxicosis In the latter the cardiac output may be doubled and yet the renal blood flow may fall to 20 per cent of its normal value The cause of this vasoconstriction is uncertain but the inability of a high spinal anæsthetic to alter the renal blood flow in established cardiac failure suggests that it may be humoral This is supported by the finding that some increase in renal blood flow occurs following the administration of the adrenaline antagonist aibenamine Large increases in renal venous pressure have been found to produce transient reductions in renal blood flow But this is not the cause of the fall in renal blood flow in cardiac failure for the renal venous pressures usually encountered are not in this high range and in chronic heart failure the venous pressure and renal blood flow may vary independently

A teleological explanation for the renal vasoconstriction which occurs with circulatory distress is that it maintains the arterial pressure and switches the available cardiac output to organs which are less able than the kidney to function with a reduced blood flow

Acute Uterine Catastrophies

There is a close association between the incidence of abortion accidental hæmorrhage and eclampsia on the one hand and severe renal ischæmia on the other Abortion is the most frequent cause of acute renal failure

In many of these conditions hæmorrhage must be partly responsible for the renal ischæmia but it is probable that occasionally other mechanisms are also involved It has been demonstrated in experimental animals that an acute rise in intra uterine pressure causes a marked fall in renal blood flow if such a mechanism is present in man it may be an important contributory factor in the causation of renal ischæmia in some of the conditions mentioned above (e.g. concealed accidental hæmorrhage).

Electrolyte and Endocrine Abnormalities

Most forms of electrolyte abnormalities cause a reduction in renal blood flow. With simple water depletion, or with combined salt and water depletion, this reduction is caused by the contraction of the blood volume. But with water intoxication due to salt loss, or excess water intake, the mechanism is obscure. Potassium deficiency and hypercalcæmia also cause a fall in renal blood flow. Initially these circulatory changes are quickly and completely reversible; if, however, they are prolonged and are associated with the development of structural changes, recovery will be incomplete.

The renal blood flow is also reduced in hyper- and hypo-adrenalism, hypopituitarism and myxœdema.

Vasoconstrictors other than those Produced by the Endocrine Glands

These consist mainly of exogenous substances and include a variety of cytotoxic poisons such as carbon tetrachloride, corrosive sublimate (mercuric chloride), propylene glycol, etc. Frequently tubular necrosis follows, both from direct action of the poison on the cells and from intense renal ischæmia.

Some infections such as Weil's disease and scrub typhus are also associated with severe reductions in renal blood flow.

Disorders of the Renal Vasculature

Atheroma of the large intrarenal arteries may occasionally lead to wedge-shaped loss of renal parenchyma and a substantial fall in renal blood flow; while hypertension (particularly the malignant form), polyarteritis nodosa, eclampsia, diabetes and amyloidosis frequently produce such obliterative changes in the arterioles and glomerular capillaries that severe fatal renal ischæmia may result. Changes in the renal vessels in diffuse lupus erythematosus and scleroderma may also lead to renal failure. The acute glomerular capillaritis of acute nephritis does not usually affect the renal blood flow, but there are occasional instances of severe renal ischæmia.

Gradual Destruction of the Renal Parenchyma as a Cause of a Decrease in Renal Blood Flow

Loss of nephrons is at first compensated for by an increased flow of blood through the remaining hypertrophied nephrons, e.g. the changes which occur following unilateral nephrectomy. Eventually, however, with further loss of nephrons the renal blood flow inevitably diminishes.

Among the conditions which have not yet been considered and which produce a gradual destruction of the renal parenchyma there are *persistent glomerular nephritis pyelonephritis polycystic disease* congenital tubular disorders renal tuberculosis and urinary tract obstruction

SOME FACTORS WHICH CAUSE RENAL HYPERÆMIA

*These include cold large protein intake hyperpyrexia sudden increase in blood volume emotion aminophylline derivatives methe-*drine magnesium sulphate polycythæmia and pregnancy In general such increases in renal blood flow are of no clinical importance though occasionally aminophylline is used to raise the renal blood flow and glomerular filtration rate when trying to obtain an adequate diuresis with diuretics

ADJUSTMENT OF THE RENAL CIRCULATION TO CHANGES IN HÆMATOCRIT

In the normal kidney the fall in hæmatocrit which occurs in anæmia is associated with a substantial decrease in renal blood flow a small reduction in plasma flow and an almost unchanged glomerular filtration rate when the hæmatocrit falls below approximately 20 however the onset of cardiac failure causes the renal ischæmia to become much more pronounced and there is a marked reduction in plasma flow *and* glomerular filtration (Fig 8 1)

Conversely the rise in hæmatocrit which occurs in polycythæmia is associated with a substantial *increase* in renal blood flow but again there is only a small reduction in plasma flow and an almost unchanged rate of glomerular filtration at hæmatocrits above approximately 75 however both the renal plasma flow and glomerular filtration rate tend to be sharply depressed

These changes suggest that the kidney is mainly concerned with the maintenance of a constant renal plasma flow and glomerular filtration and not with the total renal blood flow The mechanisms responsible for these adjustments are not known but they appear to be local in origin and unrelated to changes in cardiac output clinically the important point is that such adjustments may *take some days to complete*

In diseased kidneys these adjustments take place more slowly or not at all The result is that a perfectly justifiable transfusion for anæmia in chronic renal failure may be followed by a rapid deterioration in renal function The explanation is as *follows It has been* pointed out earlier that a reduction in glomerular filtration rate to 50 per cent of normal produces little absolute change in the blood concentrations of waste products, but with further reductions in filtration rate these concentrations rise steeply. If, therefore, owing to renal parenchymal destruction the glomerular filtration rate is low, it is clear that a further small decrease in filtration will produce a large increase in blood concentrations of waste products. Such a decrease in filtration may follow the rise in hæmatocrit which accompanies a transfusion; it is due to the failure of the renal vessels to dilate sufficiently quickly to accommodate the rising fraction of red cells; the renal plasma flow and filtration rate are automatically reduced and the patient may die of acute anuria. If it is considered necessary to treat the chronic anæmia of chronic renal failure with transfusions, it is best best to give small amounts of packed cells and not to try and raise the P. C. V. above 25. It is best to give packed red cells in order to minimise the risk of causing heart failure which is the other hazard of transfusing patients with renal failure. An estimate of glomerular function should be obtained between each transfusion.

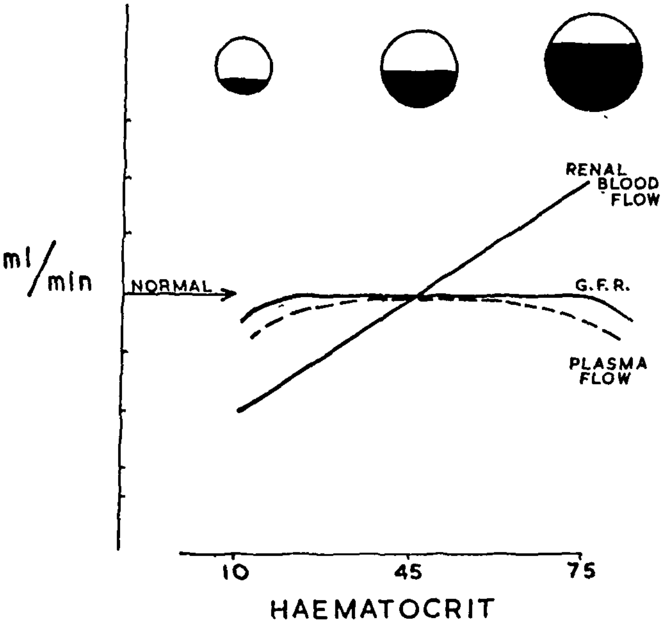

Fig. 8.1. Schema of the changes in renal blood flow, plasma flow and glomerular filtration rate which occur in the normal kidney in response to changes in hæmatocrit. The three circles illustrate what is presumably taking place in the renal vessels, i.e. the renal plasma flow remains constant because the diameter of the renal vessels varies directly with the changing fraction of red cells.

ADJUSTMENT OF THE RENAL CIRCULATION TO CHANGES IN ARTERIAL PRESSURE

The rate of blood flow is related to the arterial pressure and the resistance of the vessels, i e $F = \frac{P}{R}$ where F = blood flow, P = arterial pressure and R = vascular resistance Alterations in resistance are produced almost entirely by changes in the calibre of the vessels, i e by vasoconstriction and vasodilatation Such changes usually occur as part of a general alteration in total peripheral resistance, e g hypertension and hæmorrhage are both associated with an increase in total peripheral resistance and, in each renal vasoconstriction contributes to the increase Occasionally, however changes in renal resistance may occur which do not stem from some central demand for circulatory adjustment For instance, there are the changes in renal vascular resistance which accompany changes in hæmatocrit (see above), and the following changes which accompany alterations in arterial pressure

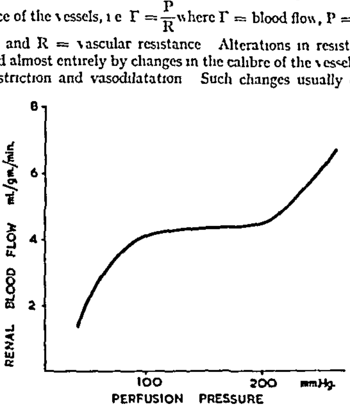

FIG 8 2 Renal circulatory autoregulation The relationship between the perfusion pressure (*i e renal artery pressure*) and the renal *blood flow* in a dog s kidney showing the relative constancy of the blood flow when the perfusion pressure is between *100* and *200 mm Hg*

It is well established that the kidney has an independent mechanism which alters the calibre of the renal vessels in response to changes in arterial pressure This relationship between the rate of renal blood

4*

flow and the arterial pressure is most easily demonstrated in the isolated perfused dog's kidney, and is illustrated in Fig. 8.2. It can be seen that over a pressure range of about 0 to 90 mm. Hg the blood flow rises with the pressure; from 90 to 200 mm. Hg the flow remains relatively unaltered; and after 200 mm. Hg the flow rises once again. The alterations in vascular lumen occur in the arteries on the afferent side of the glomerulus, for the glomerular filtration rate parallels the

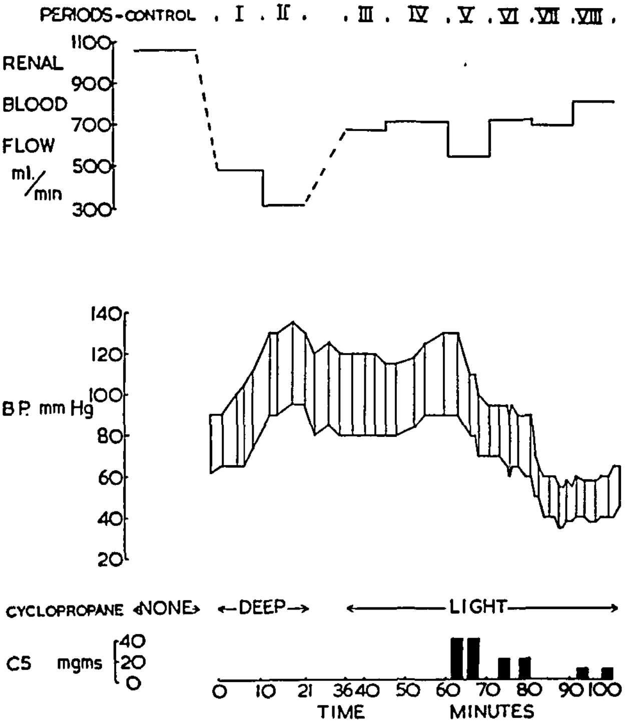

FIG. 8.3. The effect of light and deep cyclopropane, and hypotension induced with pentamethonium during light anæsthesia, on the renal blood flow. Though the arterial pressure fell to about 60/40 mm.Hg the blood flow did not change and continued to be greater than during deep anæsthesia. (Miles *et al.*, 1952, *Clin. Sci.*)

changes in the renal blood flow. The changes in the diameter of the arterial lumen are due to the innate property of the smooth muscle in the arterial walls to respond to a stretching force by a contraction, and a diminution of tension by a relaxation; a property which can be demonstrated in many sites in the body including the arteries of other organs. It is probable, for instance, that this phenomenon is responsible for the dilatation of an artery that occurs distal to the site of an obstruction. The constancy of the renal blood flow during alterations in blood pressure is known as renal circulatory autoregulation.

Indirect evidence for the presence of a similar stabilising mechanism in the renal vasculature of man has been obtained on several occasions though the exact range over which it occurs is not known It must almost certainly be over a lower range than in the dog for the mean blood pressure in man is lower than that in the dog There is some evidence that renal circulatory autoregulation in man is present down to a mean arterial pressure of about 60 mm Hg (Fig 8 3) Such observations are difficult to obtain for in most circumstances changes in arterial pressure produce a central demand for compensatory alterations in the peripheral resistance which have priority over purely local circulatory reflexes the latter are best observed following small changes in arterial pressure produced by changes in cardiac output

Teleologically this intrinsic pressure flow relationship is difficult to understand One suggestion is that it protects the glomerular filtration rate from the normal fluctuations in pressure so that the tubules are presented with a continuous steady quantity of materials As many of the factors which influence tubular function are slow to change the extent of their activity a stability of this nature may be of value

Clinically there are two aspects of this local pressure-flow relationship which are of interest The first is purely speculative does this mechanism which responds to a rise in arterial pressure by vasoconstriction ever become so disordered in disease that it causes excessive vasoconstriction at normal blood pressures? The other is more practical and is related to the treatment of hypertensive patients with hypotensive drugs When renal function is substantially normal the renal blood flow and glomerular filtration rate remain unchanged as the blood pressure falls But if there is evidence of renal damage (reduced glomerular filtration etc) before the administration of the hypotensive agent the normal pressure-flow relationship may either fail or only become manifest after a long interval In these circumstances glomerular filtration rate will fall the blood urea rise steeply and the patient may die of acute upon chronic renal failure It is always wise therefore to induce a fall in blood pressure gradually in such patients and to repeat estimations of glomerular function at frequent intervals

SHUNTS

There is no convincing evidence that true shunting of blood ever takes place in the kidney Nevertheless there are two renal circulatory phenomena which have sometimes had the word shunt applied to them One is the kidney s capacity for intense vasoconstriction and the other is the way in which it separates plasma from red cells

" Shunting " of Whole Blood

It has been claimed that in some circumstances, the cortex may become ischæmic because the blood which should have travelled to the cortex is shunted through the medulla. This conclusion was first reached from observations made on experimental animals subjected to the following stimuli: prolonged application of tourniquets to the hind limbs, bleeding, stimulation of the sciatic nerves and the administration of certain substances such as adrenaline, in large quantities. During and immediately after stimulation the renal circulation was studied by means of angiographs, injections of methylene blue, and histological sections. These techniques give an indication of the *distribution* of blood within the kidney at any one time, but are not measures of the *rate* of blood flow in any one place. It was found that the stimuli were associated with the following change in the distribution of blood; the cortex contained less and the medulla more, that is, the cortex on section was pale and the medulla was dark. Mainly from this evidence it was suggested that the ischæmia of the cortex was due to the hyperæmia of the medulla; the blood intended for the cortex having been by-passed, diverted, or shunted through the medulla.

There is much evidence however, that this assumption was unwarranted. It has been pointed out that to demonstrate that ischæmia is due to the opening of a shunt it is necessary to show that the decrease in flow in the ischæmic area is of the same order as the increase in flow in the shunt, i.e. if a large diversion of the normal cortical blood flow takes place it should be possible to demonstrate cortical ischæmia without significant reduction in renal blood flow. But when renal blood flow is measured, the cortex becomes pale and the medulla dark only when the total renal blood flow is greatly reduced. It is clear therefore, that the ischæmic pallor of the cortex cannot be due only to an increase in medullary flow, whether or not a small increase does occur. That such an increase is unlikely has been demonstrated with temperature measuring needles simultaneously recording from medulla and cortex; for when the total renal blood flow is markedly reduced by nor-adrenaline, adrenaline and stimulation of the renal nerves, the changes in temperature which take place (and which presumably reflect changes in blood flow) are the same in the two sites. It has even been suggested that when there is pallor of the cortex and congestion of the medulla it is probable that there is no blood flowing through the medulla, for it has been found that indian ink injected intravenously may sometimes fail to appear in the medulla.

The importance of the observations which led to the renal shunt hypothesis is that they showed that in certain circumstances the cortex of the kidney has a disconcerting tendency to shut off its blood supply almost completely. It is probable that in most instances of intense renal vasoconstriction the blood flow through the cortex virtually ceases while medullary blood flow continues at a very reduced rate

"Shunting" of Plasma from Red Cells

The hæmatocrit of the blood in the renal cortex is about 50 per cent of that in the large blood vessels, and in the medulla it is only 30 per cent This high proportion of plasma in the cortex is partly due to (i) its predominantly capillary bore circulation, for there is a tendency in small vessels for red cells to travel quickly down the centre in a narrow stream, while plasma passes more slowly in a wide peripheral cuff, and (ii) there is some evidence that some plasma probably lies in the interstitial space (p 8)

The even higher proportion of plasma in the medulla indicates that the blood flow through the medulla is mainly plasma The most reasonable hypothesis for this phenomenon is that the plasma is "stripped" from the red cells at the point where the afferent arterioles supplying the juxtamedullary glomeruli leave the interlobular arteries It has been shown on models that when blood flows through a tube whose branches come off at right angles (as they do from the interlobular arteries) the sleeve of plasma in the proximal tube passes selectively into the distal branches with little admixture of red cells The functional importance of this manœuvre is obscure It is possible that it contributes to a low intramedullary pO_2 (see below)

SIGNIFICANCE OF THE COUNTER-CURRENT CIRCULATION IN THE MEDULLA

It has been pointed out (p 7) that the blood supply to the medulla flows through long looped vessels (the vasa recta) which, though they are relatively wide, have walls of capillary thickness throughout their entire course And that the blood within them is obliged to flow in a counter-current fashion, first down towards the tip of the papilla and then upwards to the corticomedullary junction As the walls of the vasa recta are of capillary thickness the blood they contain is in nearly all respects in equilibrium with medullary interstitial fluid, and therefore with the fluid flowing through the thin capillary like descending limbs of Henle In addition it is very likely that at all times the fluid in the collecting ducts must also be in equilibrium with the pO_2 and Pco_2 of the medullary interstitial fluid, and there is evidence that under the influence of ADH the fluid in the collecting ducts is also in equilibrium with respect to its osmolality, urea concentration and probably hydrogen ion concentration

The importance to the medullary interstitial fluid of a counter-current flow in the vasa recta is two-fold. (i) It magnifies the *rise* in concentration which follows the transfer of any solute or gas from the tubules into the medullary interstitial fluid. (ii) It magnifies the *fall* in concentration of any solute or gas which is removed from the medullary interstitial fluid.

An example of the first consequence of the counter-current circulation was detailed on p. 44 where it was shown how it contributes to the high medullary concentrations of sodium chloride and urea, which in turn make it possible for the urine to become hypertonic. It is probable that it is also responsible for the high P_{CO_2} of alkaline urine and the low *p*H of acid urine. The most clear-cut example of the second consequence is the fact that the pO_2 of urine is lower than that of renal venous blood. This is because the initially high pO_2 of the arterial blood in the descending limb of the vasa recta is in equilibrium with the low pO_2 of the venous blood in the ascending limb; it follows that the pO_2 of the supposedly arterial blood reaching the tip of the papilla, and which is in equilibrium with the urine emerging from the collecting tubule is lower than normal arterial blood. Clinically, it is possible that this regional hypoxia is a factor in the characteristic localisation of renal tuberculosis, and in the ætiology of necrotising papillitis.

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9

THE KIDNEY AND ERYTHROPOIESIS

ANÆMIA is a constant feature of renal failure and mainly due to depressed erythropoiesis. Fig. 9.1 illustrates the average fall in hæmoglobin plotted against the rise in blood urea in patients with chronic renal failure. On the other hand, it is well-established that about 10 per cent of patients with carcinoma of the kidney have polycythæmia and that on occasion a reversible polycythæmia accompanies a hydronephrosis or polycystic kidneys. Some patients in the early stages of glomerular nephritis before the onset of renal failure may also have polycythæmia with enlarged red cell masses. Clinically therefore, it appears that loss of renal tissue is usually associated with a decrease in red cell formation, and an increase in renal tissue sometimes associated with an increased red cell formation. The connection between hydronephrosis, polycystic kidneys and glomerular nephritis with erythropoiesis is totally obscure.

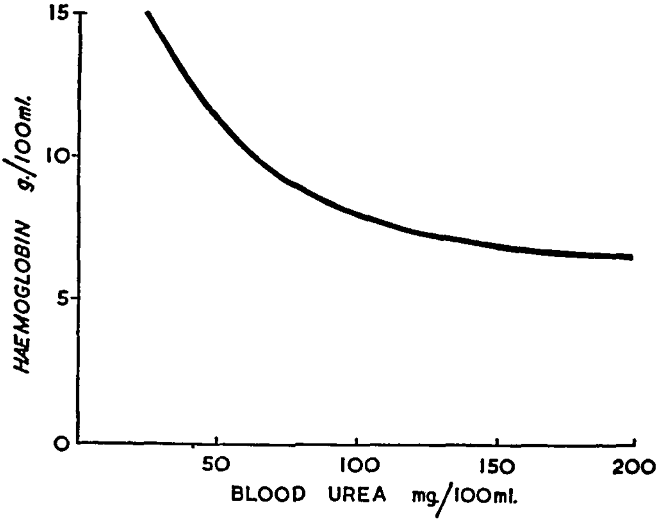

FIG. 9.1. Schema of the mean relationship between the hæmoglobin concentration and the blood urea; individual plots show a considerable scatter.

Animal experiments have demonstrated that the kidney is responsible for a circulating substance which directly stimulates the production of red cells. This substance is generally known as renal erythropoietin to distinguish it from other erythropoietic factors produced at other sites. The presence of renal erythropoietin can be detected in the blood of experimental animals. Its rate of production depends on the presence of a certain quantity of renal parenchyma regardless of its excretory efficiency. This has been shown by comparing one group of animals in which one kidney has been irradiated and the other has been removed, with another group in which one kidney has been irradiated but the other has been left in place with the cut end of its ureter stitched in the peritoneal space. The blood urea rose equally in both groups. The animals with an irradiated contracted kidney and no other renal substance became anæmic. Those with a similarly diseased kidney but in whom the other kidney was present though excreting its urine into the peritoneal space did *not* become anæmic (Fig. 9.2). It is probable that in man the anæmia of advanced renal failure is also due in part to a diminished circulating concentration of renal erythropoietin. In addition, however, there is much evidence that in contrast to the relatively acute experiments in animals mentioned above, the biochemical changes associated with advanced renal failure do affect erythropoiesis profoundly. It has been shown that erythropoiesis increases immediately after a dialysis and that if a patient is on adequate intermittent hæmodialysis there is such a persistent improvement in erythropoiesis that it is rarely necessary to give repeated transfusions.

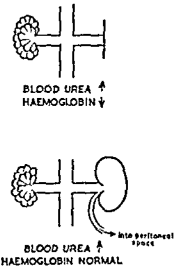

Fig. 9.2. Illustration of an experiment demonstrating that the fall in hæmoglobin in renal failure is not due to the accumulation of waste products. Right kidney irradiated. (Osnes 1959 *Brit. med. J.*)

Renal polycythæmia should be suspected in a patient whose polycythæmia is associated with a normal arterial saturation but with no increase in white cells or platelets and no enlargement of the spleen. If, in addition, there is an episode of hæmaturia the diagnosis becomes increasingly likely. Occasionally there is a tendency to think that the hæmaturia has been caused by the polycythæmia when, in fact, it is due to the renal lesion responsible for the polycythæmia. About 1 per cent of all patients with an initial diagnosis of polycythæmia vera are subsequently found to have renal polycythæmia. A few of these have a palpable spleen, which is misleading.

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10

THE KIDNEY AND HYPERTENSION

There are five important points to note when considering the relationship between the kidney and hypertension

(1) Renal mechanisms concerned with hypertension have mainly been studied in animals by partially occluding the main trunk of one or both renal arteries

(2) *Partial occlusion of a main renal artery in man causes hypertension*

(3) Renal disease in man is often associated with hypertension particularly when disease occludes some of the larger intrarenal arteries

(4) Hypertension in man causes occlusive lesions of the renal arterial tree particularly the smaller arteries and arterioles and it also causes disturbances of renal function

(5) *There is as yet no evidence that essential hypertension in man is due to renal dysfunction*

EXPERIMENTAL HYPERTENSION

Renal Hypertension

It has been firmly established in experimental animals that partial occlusion of the renal artery is followed by hypertension In some animals both renal arteries must be occluded whereas in the rat it is sufficient to occlude only one renal artery (Fig 10 1) Hypertension does not appear to be due to renal ischaemia for it can be induced by an occlusion which does not interfere with renal blood flow An unchanged renal blood flow despite partial occlusion of the renal artery may at first seem paradoxical but it is probably maintained by renal circu

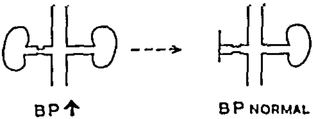

Fig 10 1 Renal hypertension.

latory autoregulation the phenomenon discussed in a previous section (p. 97). The hypertension is probably due to the fall in perfusion pressure, though there is also evidence that hypertension may follow a partial occlusion of the renal artery even if the occlusion is adjusted so that the mean renal arterial pressure distal to the point of occlusion remains unchanged. Renal artery occlusion causes the juxta glomerular apparatus to release renin into the general circulation which reacts with plasma angiotensinogen to form a vasoconstrictor angiotensin. There is no doubt that this mechanism can cause transient hypertension, but it is less certain that the *maintained* hypertension of renal artery occlusion is unlikely to be due to an increase in circulating angiotensin, for after a few weeks there is no evidence of an over active renin mechanism.

There are two other renal manipulations which cause a rise in blood pressure. One is known as *vicious circle renal hypertension*, and the other as *renoprival hypertension* (to distinguish them from the hypertension which follows renal artery occlusion, i.e. *renal hypertension*). It is possible that the mechanisms which cause the blood pressure to rise in these manœuvres may also be concerned in maintaining the rise in blood pressure which follows renal artery occlusion.

Vicious Circle Renal Hypertension

This form of hypertension is intimately connected with renal hypertension and occurs in the following circumstances. If renal

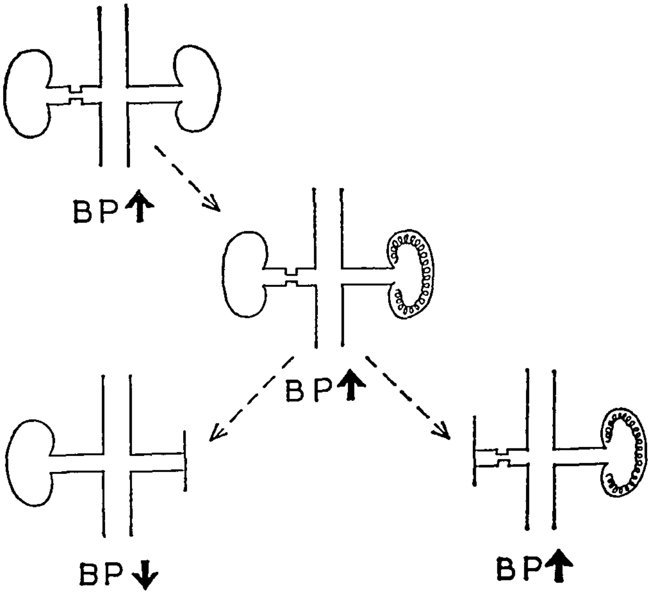

FIG. 10.2. Vicious circle hypertension.

hypertension is induced in the rat by occluding only one renal artery, the subsequent removal of the occlusion or of the occluded kidney may or may not be followed by a return of the blood pressure to normal The deciding factor is the extent of hypertensive vascular damage present in the untouched kidney (Fig 10 2) Once again the mechanism responsible for the persistent hypertension is unknown As it is related to the degree of vascular damage it has been suggested that perhaps the mechanism is the same as in renal hypertension the occlusion being produced by hypertensive vascular changes throughout the periphery of the renal arterial bed If such a self perpetuating hypertensive mechanism occurs in man it is clearly of the utmost therapeutic importance It has been suggested that the perpetuation of the hypertension is not due to an abnormality of the vessels of the untouched kidney but to an adaptation of the circulatory baroreceptors to the higher levels of arterial pressure This hypothesis has been eliminated by demonstrating that however long a rise in blood pressure has been maintained by partially occluding one renal artery it can always be lowered by removing the occlusion and excising the untouched kidney (Fig 10 2)

Renoprival Hypertension

As the name implies this form of hypertension follows bilateral nephrectomy It cannot therefore be due to any pressor substance elaborated by the kidney The alternatives are that it is due to (1) an extra renal pressor substance which is usually disposed of by the intact kidney (2) the absence of a vasodilator normally produced by the kidney or (3) to salt and water retention due to inadequate dialysis Salt and water retention is probably the commonest cause Nevertheless it has been demonstrated that the medulla contains a substance which lowers the blood pressure and it has been claimed that hyper tension does not follow implantation of both ureters into the bowel (Fig 10 3) or into the inferior vena cava

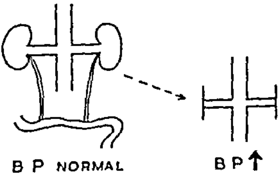

Fig 10 3 Renoprival hypertension

Experimental Hypertension and Perirenal Compression

If one kidney is surrounded by some hard unyielding substance such as colloidon, the blood pressure rises rapidly and the animal dies of malignant hypertension within a few days. The mechanism which causes this rise in blood pressure is totally obscure. It is not related to a decrease in pulse pressure for the diminished distensibility of the kidney in these conditions causes a pronounced increase in intrarenal pulse pressure.

Experimental Hypertension and Adrenal Function

Angiotensin not only causes arteriolar constriction but also stimulates the adrenal cortex to secrete aldosterone. Partial occlusion of the renal artery is therefore associated with a raised concentration of circulating aldosterone, some degree of sodium retention, and a urinary leak of potassium. It has recently been established that the sodium retention (or perhaps the associated water retention) potentiates the effect of the angiotensin. This may partly account for the paradox that though partial occlusion of the renal artery causes a rise in arterial pressure which is initially associated with an increased circulating concentration of renin and angiotensin, later the pressure remains raised though there is now no evidence of an increased production of renin.

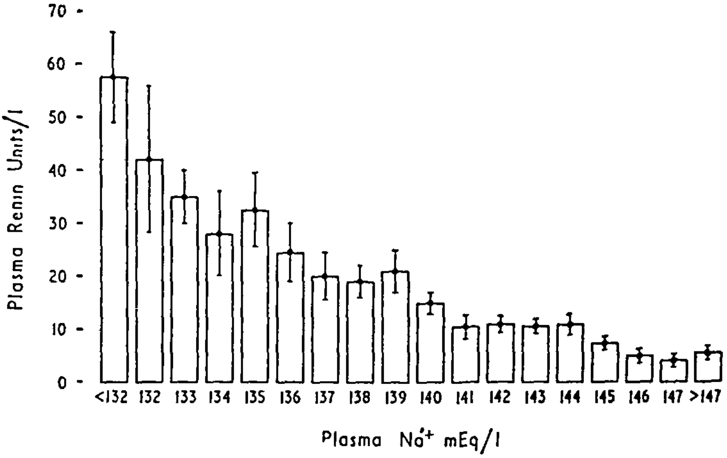

FIG. 10 4 Relationship between plasma renin and sodium concentrations in 253 patients with hypertension (Brown *et al.*, 1965, *Brit. med. J.*)

It is also interesting that when sodium and water retention is produced by an excess of aldosterone secondary to a prolonged experimental infusion of angiotensin the concentration of plasma sodium *falls* whereas an infusion of aldosterone causes a *rise* in plasma sodium.

The most striking clinical counterpart of the experimental findings is the severe secondary aldosteronism that accompanies the sudden onset of partial or complete occlusion of the renal artery. It can be so pronounced that the most prominent clinical feature may not be the rise in blood pressure but the thirst and polyuria caused by the negative potassium balance due to the renal loss of potassium

In addition it has been established that in conformity with the fall in plasma sodium which accompanies an infusion of angiotensin, the concentration of plasma renin in patients suffering from hypertension is inversely related to the plasma sodium concentration (Fig 10 4). The most striking examples are patients with malignant hypertension who have a low concentration of plasma sodium and potassium and very high rates of secretion of aldosterone, often greater than in primary aldosteronism.

Correlation Between Experimental and Clinical Findings

Statistically it is evident that in man renal disease is associated with hypertension; it is not unreasonable therefore, to suspect that some, if not all, the renal mechanisms which have been shown to produce hypertension in animals may eventually be proved to have their clinical counterpart. Some parallels can already be drawn

ALTERATIONS IN PULSE PRESSURE

Following hæmorrhage, or acute reductions of the extracellular volume by vomiting and diarrhœa, the pulse pressure diminishes whether or not there is a fall in mean arterial pressure; in these circumstances the renin mechanism is stimulated and the maintenance of the blood pressure is in part controlled by an increased quantity of circulating angiotensin.

A reduced pulse pressure to the renal arterial tree also occurs in coarctation of the aorta. In this condition, though there is no evidence that the renin mechanism is hyperactive or that the rate of renal blood flow is abnormal, it is nevertheless probable that the hypertension is renal in origin and that the stimulus to the kidney is the diminished pulse pressure. Unfortunately the best evidence that the hypertension of coarctation of the aorta is renal is again experimental It has been shown that artificial "coarctation" of the aorta in an animal only induces hypertension when there is a kidney below the "coarctation," and that the hypertension can be abolished by transplanting the kidney into the neck.

Chronic anæmia provides a good example that a reduced renal blood flow is an unlikely cause of hypertension, for the renal blood flow may be decreased considerably, yet a raised arterial pressure is most unusual; the pulse pressure in anæmia, however, is much increased.

RENAL HYPERTENSION

Hypertension due to partial occlusion of one or both renal arteries is an exact clinical counterpart to the animal experiments. The mechanisms which cause the blood pressure to rise when there is a primary disease of the kidney is unknown. It is attractive to see an analogy with experimental renal hypertension, and in some conditions, e.g. renal polyarteritis or persistent pyelonephritis, it is possible to show unequivocal occlusive changes in the renal arterial tree. The difficulty about accepting this occlusive theory wholeheartedly is that occasionally severe vascular changes with extensive destruction of the renal parenchyma may be associated with a normal blood pressure. This is seen sometimes in young persons dying with small contracted kidneys, or at any age in renal amyloidosis.

VICIOUS CIRCLE HYPERTENSION

The mechanism responsible for this form of hypertension may aggravate every case of hypertension in man, but it is only possible to demonstrate its presence in patients suffering from hypertension and unilateral renal disease. In most of these, removal of the diseased kidney does not lower the blood pressure, and it is probable that this is because the hypertension has produced irreversible renal vascular changes in the opposite kidney. This interpretation is quite convincing, for when a unilateral lesion is of short duration the blood pressure often returns to normal following a nephrectomy.

It is clear that if there is a strong suggestion that vicious circle hypertension occurs in unilateral renal disease, it is probable that the same mechanism perpetuates and aggravates hypertension in bilateral renal disease.

PERIRENAL COMPRESSION

Occasionally a perirenal hæmatoma following an injury may cause hypertension. The arterial pressure rises within a few weeks of the accident but it can be lowered by removing the organising clot.

HYPERTENSIVE VASCULAR DISEASE IN MAN

Structural Changes

Hypertension, however caused, eventually leads to changes in renal structure and function; the structural changes are sometimes known as nephrosclerosis. Initially these mainly occur in the vessels, but, as the lesions progress there are secondary ischæmic changes in the nephrons The vascular changes may be either acute or chronic The acute changes are found in association with *malignant hypertension*, *they consist* of gross thickening of the intima of the smaller arteries and focal necrosis of arterioles The chronic lesions are found mainly in association with non malignant hypertension they consist mainly of a less marked thickening of the whole wall of the smaller arteries

Acute Changes

The most important change is a thickening of the intima of the comparatively large intralobular arteries so that their lumens become extremely small In younger patients this is due to a cellular hyperplasia in which there is no collagen or elastic fibres In older patients *it is due to an increased quantity of fibro elastic tissue similar to that* found in much smaller quantities in non malignant hypertension There is little doubt that this subintimal proliferation is due directly to the rise in blood pressure Teleologically it is reasonable that the normal mechanism whereby the rise in blood pressure induces a renal functional vasoconstriction (p 97) should be reinforced by a structural *narrowing but the exuberance of this support is sometimes lethal*

The other acute vascular change consists of localised areas of necrosis of the whole thickness and circumference of an arteriole These necrotic lesions contain large amounts of fibrin so that the change is often called fibrinoid necrosis

Subintimal proliferation occludes the smaller arteries At first this produces only a thickening of glomerular capillary walls but subsequently the glomeruli atrophy and are replaced by collagen Arteriolar necrosis may be associated with focal areas of acute necrosis in the glomeruli which can be recognised as collections of structureless eosin staining material containing disintegrating nuclei and narrow capillary lumens

There is a strong suggestion that the principal factor which determines whether the lesions accompanying the rise in blood pressure are acute or chronic is a difference in the state of the vessels and not the height of the pressure *The nature of this difference is unknown Acute changes are more likely if the rate of rise in blood pressure is* rapid or if the hypertension is initially caused by a renal disease such as glomerular nephritis or pyelonephritis

Chronic Changes

The chronic vascular changes which are found characteristically in prolonged hypertension may also be found in patients with normal blood pressure There is a generalised narrowing of the arterioles and intralobular arteries with fibro-elastic tissue and the deposition of an eosinophilic structureless material. Gradually complete occlusion of the lumen may occur and a patchy ischæmia of increasing severity develops. This process may, of course, develop in previously normal kidneys, and may occasionally be severe enough to cause renal failure; but it also complicates most longstanding cases of renal disease, when it then contributes to, and accelerates, the kidney's eventual destruction. In the larger arteries these chronic vascular lesions eventually cause focal wedge-shaped areas of degeneration situated between relatively normal renal tissue. In the affected areas the glomeruli tend to be crowded together. The glomerular tufts show a diffuse thickening with collagen accompanied by a similar thickening of the glomerular capsule; eventually the collagenised tuft and capsule become fused, the capillary lumens are obliterated and the glomerulus is replaced by fibrous tissues. At first, the tubules between these glomeruli lose their lumens, but the cells show little change so that the glomeruli appear to be packed in solid wedges of relatively normal cells. Later the cells atrophy and there is fibrous tissue replacement. When these vascular changes are far advanced there may be no normal tissue left and it may then be impossible, histologically, to distinguish them from the end stages of such chronic renal diseases as glomerular nephritis or pyelonephritis, in which vascular changes are only a complication.

Functional Changes

The only consistent abnormality is in the handling of sodium chloride. Though patients with a high blood pressure are in normal salt balance they have a remarkable tendency suddenly to excrete abnormally large quantities of salt in response to certain stimuli, e.g. an osmotic diuresis induced by mannitol, the intravenous administration of angiotensin, or certain emotional situations (Fig. 10.5). The cause of this phenomenon is not understood. It is not due to any abnormality in the extracellular fluid or blood volume. There is some evidence that it is related in part to the direct effect of the raised arterial pressure itself on the kidney (p. 69). In the early stages, before there is any marked change in renal blood flow or glomerular filtration rate, it is sometimes possible to demonstrate an impaired ability to dilute or alkalinise the urine. In addition many patients with hypertension have an impaired ability to excrete uric acid which causes a rise in serum uric acid. This phenomenon is associated with a higher incidence of cerebrovascular and ischæmic heart disease. None of these abnormalities of tubular function has been explained.

Otherwise essential hypertension initially causes little disturbance

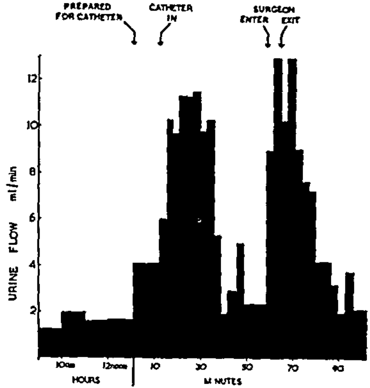

FIG 10 5 The effect on urine flow of (1) catheterising the bladder and (2) a brief interview with a surgeon in a patient suffering from hypertension The sudden increases in urine flow were due to sudden increases in sodium excretion (Miles and de Wardener 1953 *Lancet*)

in renal function renal blood flow measurements show renal vasoconstriction with a normal rate of flow while complex and speculative calculations suggest that the efferent glomerular arteriole constricts to a greater extent than the afferent and that this is one of the reasons why glomerular filtration rate also remains unchanged Renal biopsies at this time show *no abnormality of structure* Gradually renal blood flow and glomerular filtration decrease the latter always to a lesser extent than the former small amounts of protein appear in the urine and there is some diminution of the ability to concentrate, at this stage renal biopsies show hypertensive vascular changes with scattered local changes in the glomeruli Unless malignant hypertension supervenes it is unusual for these changes to become sufficiently extensive to cause symptomatic renal failure With malignant hypertension proteinuria increases and the urine contains many red cells and granular casts tubular capacity to concentrate is lost renal blood flow and glomerular filtration rate fall precipitously and renal failure rapidly develops If the blood pressure can be lowered without immediately aggravating the renal failure most of the acute structural and functional changes disappear.

UNILATERAL RENAL DISEASE ASSOCIATED WITH HYPERTENSION

The importance of this group of patients is that in a few the hypertension may be due to the renal lesion, and that nephrectomy, or correction of an obstruction or by-pass of a renal arterial occlusion may cure the hypertension. On the other hand, only approximately 0·25 per cent of all patients with a raised diastolic pressure are found to have a unilateral renal lesion which surgery can benefit. It is also important to note that demonstrable partial occlusion of the renal artery may not be associated with hypertension; or that if partial occlusion of the renal artery is associated with hypertension, the occlusion may not be its cause. Occlusion of the renal arterial tree may be either in the main renal artery or its main segmental branches before they enter the parenchyma of the kidney, or in the smaller arteries within the renal parenchyma. The lesions in the main artery and its branches include atheromatous plaques, " fibromuscular hyperplasia," aneurysm and embolisms, and external compression from a tumour. Parenchymatous renal lesions include chronic pyelonephritis, irradiation of the kidney and tuberculosis of the kidney.

Clinical Features

On the whole there is little to distinguish these patients from the other 99·75 per cent of patients suffering from hypertension. There may be a recent history of abdominal trauma, emboli or thrombi in other sites, or of pain in the flank or loin. The diastolic pressure may have been noted to rise rapidly and the patient may complain of thirst and polyuria. Stenosis of the renal artery is sometimes associated with a systolic murmur which is heard best posteriorly over the affected artery. There is also a slender statistical connection between occlusive disease of the renal arteries, a negative family history of hypertension, an onset of hypertension under 30 years or after 55 years of age, and the presence of proteinuria.

Renal Structure

The characteristic appearance in the parenchyma is best seen in occlusion of the main renal artery or its branches. The tubules become small with narrow lumens and shrunken cuboidal cells. The glomeruli remain relatively unchanged but are crowded together because of the tubular atrophy On the other hand, the arterioles are normal in striking contrast to the arterioles from the opposite kidney which is *being perfused with a raised arterial pressure*

Renal Function

Experimentally partial occlusion of a renal artery perfusing functioning renal parenchyma causes a variable fall in renal plasma flow and glomerular filtration rate The most characteristic change however is a great increase in tubular reabsorption of sodium in the proximal tubule This is probably due to the lowering of the peritubular venous capillary pressure (p 70) *The increase in sodium reabsorption* causes a marked increase in water reabsorption from the proximal tubule This has two consequences it reduces the urine flow and raises the concentration of those substances in the tubule lumen which are not reabsorbed i e creatinine inulin PAH or Hypaque A kidney being *perfused by a partially occluded renal artery therefore will produce* urine at a slow rate which nevertheless contains a lower concentration of sodium than that from the opposite kidney but a higher concentration of creatinine inulin or PAH Clearly the pattern is only discernible if the process is unilateral or at least more pronounced on one side *than the other If this phenomenon can be demonstrated it is highly* probable that a considerable proportion of functioning proximal tubules are being perfused at a low pressure It is then justifiable to imply that a similar proportion of functioning juxta glomerular apparati are also being perfused at a low pressure and to conclude therefore that at least *part of the hypertension is probably due to partial occlusion of the renal* arteries The opposite also holds The unequivocal demonstration of a unilateral renal abnormality or renal artery stenosis in the absence of this characteristic functional pattern implies that either the occlusion to the renal arteries is not sufficient to lower the perfusion pressure or *that the low perfusion pressure is not affecting functioning proximal* tubules and therefore functioning juxta glomerular apparati

Diagnosis

The methods available include an intravenous pyelogram (I V P) aortography individual renal functional studies renal biopsy isotope renogram and renal vein renin concentration *The intensity with which these techniques are used depend on how suggestive are the clinical* features the age of the patient and what it is considered it might be appropriate to do if occlusive renal arterial disease were found

I V P It is imperative that an intravenous pyelogram be performed on any patient in *whom one or more of the clinical features described* above is present. An I.V.P. in such a patient must be performed with a rapid infusion of contrast medium and the taking of films at 15 sec., 1, 2 and 3 min. after the injection, in addition to the other films taken at 5, 10 and 20 min. Ureteric compression must not be used during the first few minutes. If there is unilateral occlusion of the renal arterial tree the contrast medium appears first in the pelvis and ureter of the unaffected kidney, and in the first few minutes the contrast medium on the affected side is *less dense* than on the " normal " side. This is due to the slow urine flow and reduced glomerular filtration rate of the affected kidney. Ten to 20 minutes later, however, the picture is reversed. Because of the increased sodium and water reabsorption which accompanies the vascular occlusion the contrast medium on the affected side is now *denser* than on the normal side. At this time it is possible to compare the lengths of the two kidneys; a difference greater than 1·5 cm. is abnormal and nearly always accompanies an occlusion of the renal artery.

These characteristic findings can sometimes be made more distinct by performing the pyelogram during a water of a urea-saline diuresis. If the I.V.P. is normal and the clinical features not particularly suggestive of occlusive arterial disease no further test need be carried out.

Aortogram. It is doubtful if this should be performed unless there is very strong clinical suspicion of a renal vascular cause for the hypertension or the intravenous pyelogram suggests that it is a likely possibility.

Individual renal functional studies. Ureteric catheters are introduced via a cystoscope into each ureter and urine collected from each kidney during the intravenous administration of urea, saline and vasopressin. The characteristic finding is that the affected kidney has a urine flow 50 per cent less than on the other side, with at least a 20 per cent increase in creatinine concentration and a 20 per cent reduction in sodium concentration.

This test need only be performed when (*a*) the I.V.P. and aortogram suggest that there is occlusion of the renal arterial tree but the pattern of change in the I.V.P. does not define the characteristic functional abnormaility sufficiently well, and (*b*) if there is some doubt about the functional capacity of the opposite kidney. Individual renal studies are difficult to perform in a reliable way and can give rise to painful complications. They should be avoided as much as possible.

Renal Biopsy. If this test is used a sample should be obtained from both sides. It is the contrast between the two sides which is diagnostic.

Isotope Renogram. The popularity of this test in the diagnosis of occlusive vascular disease is due more to its convenience than to its reliability.

Renin concentration in the renal vein. Blood is obtained from both renal veins. Occlusive renal arterial disease is reported to be associated with raised concentration of renin in the venous blood from the affected side. This seems a most definitive test but unfortunately as very few centres can measure renin accurately its value is still to be established.

Treatment

If the patient is young and the disease is unilateral it is justifiable to attempt either to correct or by-pass the occlusion or to perform a nephrectomy. In the majority of instances, however, the patients are middle-aged or elderly and the cause of the occlusion is atheroma. The proper treatment is then less obvious. If the hypertension can be controlled satisfactorily with hypotensive drugs it is debatable whether the patient should be subjected to an operation.

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11

THE KIDNEY AND ŒDEMA

NORMAL CONTROL OF THE VOLUME AND CONCENTRATION OF BODY FLUIDS

WATER is added to body fluids principally by oral intake, but there is also a small contribution of 200–300 ml a day which is an end product of metabolism Water is lost via the skin, lungs and kidneys, loss from the gut is negligible unless there is vomiting, diarrhœa or a fistula *The intake of water is controlled by thirst, while its output is* adjusted by the kidneys, the amount of water lost from the skin and respiratory tract is mainly dependent on atmospheric conditions and is thus beyond the body's internal authority

Thirst

The sensation of thirst appears to originate in the hypothalamus, it is influenced by a wide variety of factors, the two most important being the osmolality of the extracellular fluid, and the blood volume The first can easily be demonstrated by administering hypertonic saline, and the second by performing a substantial venesection It is *probable that the thirst centre is directly stimulated by changes in* osmolality, but it is not known how it is aware of changes in blood volume

Renal Control of Extracellular Fluid Tonicity

The control of water output by the kidney is intimately connected with the control of sodium chloride excretion, both varying with the need to keep the tonicity of body fluids and the blood volume within normal limits It is probable that the osmolality of the intra- and extracellular fluids is the same, so that it is possible for the kidney *to maintain tonicity of body fluids simply by adjusting the osmolality* of the extracellular fluid Theoretically this could be achieved by altering the urinary excretion of either water or salt, but in practice it is done mainly by altering the excretion of water The neurohypophysis responds to changes in plasma osmolality by rapid alterations *in the rate at which the antidiuretic hormone (ADH) is secreted* into the circulation, and ADH in turn controls the concentration of the urine and therefore, the volume of urine that is excreted For instance, a drink of water lowers plasma osmolality; this inhibits ADH production by the neurohypophysis and within 20–30 minutes the urine becomes hypotonic, whereas with fluid deprivation and a rise in plasma osmolality the mechanism is reversed.

Renal Control of Extracellular Fluid and Blood Volume

Changes in blood volume induce alterations in both sodium and water excretion. It is clear that if the tonicity of body fluids is to remain constant the ratio of salt to water released or retained must be in isotonic proportions. This synchronisation of the different mechanisms which control salt and water excretion can be demonstrated by bleeding a normal subject, when there is a prompt and simultaneous *decrease* in both salt and water excretion; or, conversely, by administering blood or a " plasma expander " such as albumin when there is a simultaneous *increase* in salt and water excretion.

The efferent mechanism responsible for changes in water excretion consists mainly in altering the rate of secretion of antidiuretic hormone (ADH); those mechanisms responsible for the changes in salt excretion are more obscure. There is now considerable evidence that changes in sodium excretion which originate from a change in blood volume are due almost entirely to changes in tubular reabsorption of sodium. When blood volume changes are rapid, the mechanisms responsible for this diminished tubular reabsorption include changes in peritubular venous capillary pressure (p. 70), and changes in the circulating concentration of an unidentified hormone. When blood volume changes are more prolonged, changes in the circulating concentration of aldosterone become important.

The afferent stimulus produced by a change in blood volume is generally considered to be a change in pulse pressure in vascular compartments from the walls of which afferent impulses travel centrally. The carotid baroreceptors have been shown to be such a site for the control of aldosterone secretion. It is not known where the afferent stimuli originate which control ADH secretion.

GENERALISED ŒDEMA

Generalised œdema is due to retention of salt and water by the kidneys. This occurs in cardiac failure, malnutrition, the nephrotic syndrome and chronic liver failure. It seems that salt and water retention in all these conditions is due, in part at least, to the same mechanisms which cause a decreased salt and water excretion when the blood volume is reduced. There is a reduction in blood volume with malnutrition, the nephrotic syndrome and chronic liver failure. In cardiac failure, however, the blood volume is usually *greater than normal and some* other afferent stimulus must be involved It does not appear to be anoxæmia or raised venous pressure The most likely hypothesis for which there is as yet little evidence is that when the heart fails this is a change in the impulses coming from afferent fibres situated in the myocardium and that these are due to alterations in pulse pressure within the chambers of the heart It is suggested that these impulses *then travel to the same centre in the central nervous system which* controls salt and water excretion *in response to changes in blood* volume A high urinary excretion of aldosterone has been demonstrated in the nephrotic syndrome cardiac failure and chronic liver failure Nevertheless there is evidence that in these conditions other unidentified salt retaining mechanisms are also active

There is a considerable amount of evidence to demonstrate that *aldosterone is a minor factor in the type of salt retention which leads* to œdema (i) There is no œdema in primary aldosteronism (ii) In a normal subject sodium retention ceases after 3–10 days of continuous aldosterone administration (iii) Cardiac failure with œdema can occur after total bilateral adrenalectomy (iv) Inhibition of aldosterone secretion with amphenone or aldosterone antagonists such as spironolactone often fail to produce a diuresis in patients with œdema *Conversely the intravenous administration of saline in large amounts to patients with* Addison s disease maintained on 9α fluorohydrocortisone (a potent sodium retaining steroid) produces a salt diuresis indicating that there is a mechanism which releases salt which can overcome the effect of salt retaining steroids

In the three conditions in which there is a negative protein balance i e malnutrition the nephrotic syndrome and chronic liver failure *the reduction in blood volume is due to the diminution in the total* number of plasma protein molecules as then less water can be retained within the vascular compartment It follows that even if the volume of extracellular fluid remains unchanged a greater proportion will lie in the interstitial space If at the same time the concentration of plasma proteins falls (which is usually does) and the plasma protein osmotic pressure is reduced *there is an increased filtration at all capillary surfaces* and the partitioning of water and salt between the interstitial fluid and the vascular compartment is again disturbed so that there is an increase in the volume of interstitial fluid When the volume of interstitial fluid reaches a certain level it becomes clinically evident as œdema Fig 11 1 illustrates the ætiology and probable mechanisms responsible for generalised œdema

It is *necessary to mention that many patients suffering from* generalised œdema have a reduced renal blood flow and glomerular filtration rate, and at one time it was suggested that the diminished salt excretion was directly related to the decreased filtration rate. This hypothesis was consistent with much animal work, particularly in dogs, in which it seems beyond doubt that acute changes in filtration

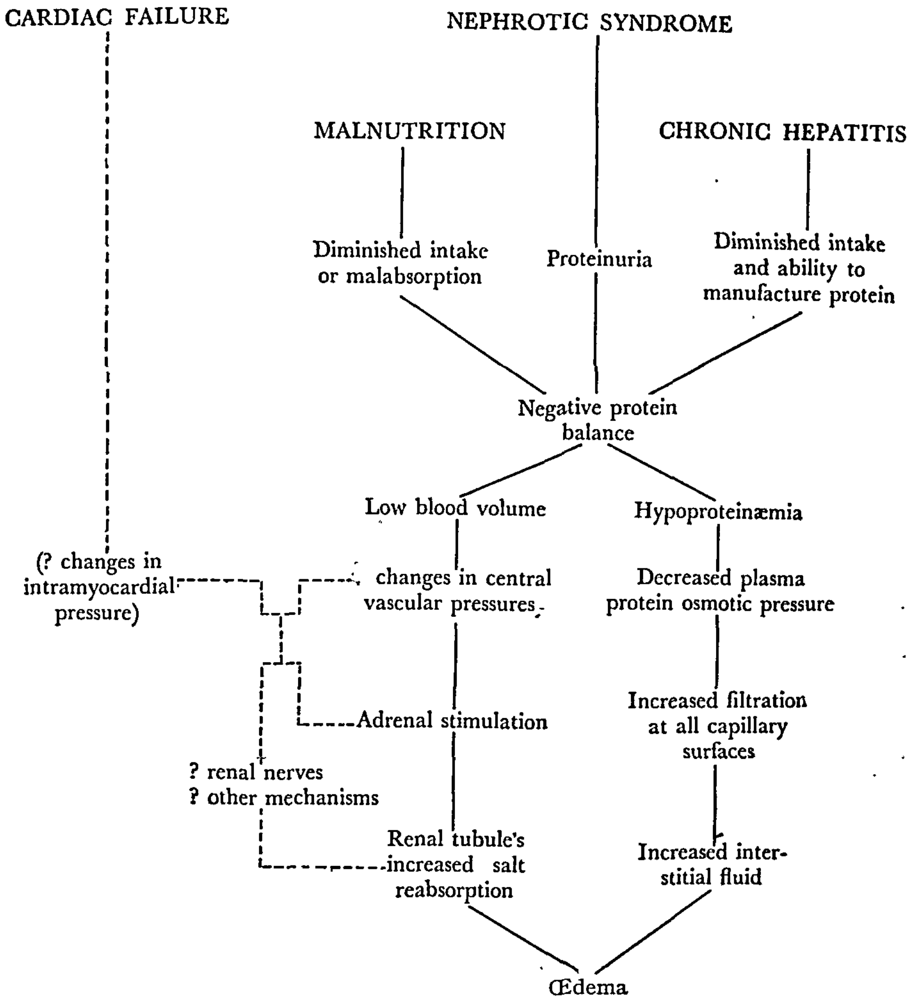
CARDIAC FAILURE
NEPHROTIC SYNDROME
MALNUTRITION
CHRONIC HEPATITIS
Diminished intake or malabsorption
Proteinuria
Diminished intake and ability to manufacture protein
Negative protein balance
Low blood volume
Hypoproteinæmia
(? changes in intramyocardial pressure)
changes in central vascular pressures
Decreased plasma protein osmotic pressure
Adrenal stimulation
Increased filtration at all capillary surfaces
? renal nerves
? other mechanisms
Renal tubule's increased salt reabsorption
Increased interstitial fluid
Œdema

FIG. 11.1. The ætiology and some of the mechanisms responsible for generalised œdema.

rate are responsible for striking changes in salt excretion. But it is now clear that prolonged changes in glomerular filtration rate, such as are found in clinical conditions, are of not great consequence to the excretion of electrolytes. For instance, the removal of one kidney is followed by a normal electrolyte balance, although the filtration rate, in spite of compensatory hypertrophy of the remaining kidney, remains lower than before Patients with cardiac failure have been observed to have a diuresis of salt and water before any change is apparent in the renal blood flow or filtration rate, and a similar dissociation has been reported in patients recovering from acute nephritis Again, patients with advanced renal disease frequently have a filtration rate which is less than 10 ml per min and may yet be in normal salt and water balance

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12

THE NEPHROTIC SYNDROME

A NEPHROTIC* syndrome is a clinical state in which there is a combination of œdema, proteinuria and hypoproteinæmia, irrespective of ætiology or any other clinical features. This definition stresses the occasional clinical similarities of many unrelated diseases, for the nephrotic syndrome may occur in any of the following conditions: glomerular nephritis, amyloid disease, diabetes, polyarteritis nodosa, chronic pyelonephritis, disseminated lupus erythematosus, thrombosis of the renal veins, the administration of certain drugs such as troxidone (Tridione) and mercury, (teething powders or diuretics), and with anaphylactoid purpura; it may also occur as a congenital condition.

Structural Changes

The changes depend upon the ætiology of the nephrotic syndrome. Biopsy studies with the light microscope have shown that the nephrotic syndrome can occur without any changes in the glomerulus. Observations with the electron microscope, however, have shown that even in those biopsies in which there are no changes to be seen with the light microscope there are unequivocal alterations in the cytoplasmic extensions of the epithelial cells (p. 3), and in the basement membrane.

The tubule changes vary widely; they are not marked in the proximal tubules. Some are dilated and lined with flattened pale cells with poorly staining nuclei, while others appear to be occluded by large swollen tubule cells containing vacuoles and much fatty material. Often there are no changes apparent on light microscopy.

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* The term " nephrosis " is gradually becoming extinct. Clinicians have continually disagreed on an exact clinical definition, and pathologists have used the word in a morphological sense to describe any " degenerative " condition of the kidney which they found difficult to classify. Jean Oliver's well-known broadside against the use of the word " nephrosis " begins ". . . that etymologically absurd and conceptually obfuscatory term nephrosis." He continues: " This curious barbarism was introduced by the clinician Friedrich Muller, apparently because to his ear ' osis ' had the proper antithetical ring to ' itis ' and so seemed appropriate as a sort of counter-term to nephritis. The suffix ' osis ' had at the time an accepted meaning, ' to be full of,' as in lipoidosis or carcinomatosis, so that by all the custom and usage of medical nomenclature nephrosis means ' full of kidney.' On this etymologically nonsensical basis an elaborate superstructure of vague and varied conceptual meaning has developed. . . ."

At the moment " a nephrotic syndrome " has an accepted and precise clinical definition. For this reason the term " nephrotic syndrome " has been used here, but perhaps in time it will be described by a more rational substitute such as " proteinuric hypoproteinæmia." " Protein losing kidney " has also been suggested.

Functional Changes

In addition to œdema, proteinuria and hypoproteinæmia, the blood lipids are usually raised and the serum calcium reduced, and there may be changes in renal function

Œdema is due to the contraction of the blood volume and the diminished plasma protein osmotic pressure, and both stem from a decreased quantity of circulating plasma proteins It is sometimes possible to observe over a prolonged period, a plasma albumin concentration of less than 1 g /100 ml in young patients who have little or no œdema Such patients' kidneys are clearly not retaining sodium The absence of œdema in such patients illustrates nicely the trivial importance of the plasma protein osmotic pressure on the formation of œdema Presumably in such patients the increased capillary filtration which must accompany the fall in plasma protein osmotic pressure is compensated for, either by some peripheral vascular adjustment which causes a fall in hydrostatic capillary pressure, or the lymphatic system drains away the increased formation of interstitial fluid

As the plasma proteins are qualitatively normal the protein disturbance is simply one of negative balance, this is also shown by the marked diminution in muscle protein, which is manifest as muscle wasting The possible mechanisms for the negative protein balance are (i) loss of protein in the urine, (ii) increased protein breakdown, and (iii) decreased protein synthesis There is certainly proteinuria so the problem is narrowed down to whether it is the only cause of the negative protein balance or whether there is, in addition, increased protein breakdown, or decreased protein synthesis It appears from isotope studies with iodine labelled albumin that in some cases there is indeed an increased rate of protein breakdown though in others it may be normal or low Protein synthesis has also been found to be variable The most œdematous patients often have a high urinary excretion of protein together with an increased breakdown and a diminished synthesis

The cause of the proteinuria is also in doubt The possibilities are either an increased glomerular capillary permeability or a decreased capacity of the tubules to reabsorb protein There is some evidence that though occasionally there is a suggestion of impaired reabsorption, usually proteinuria is due to increased glomerular permeability Assuming this to be correct, it follows that the increased quantity of protein which leaks into the tubule probably provokes the tubular protein reabsorbing mechanisms to increased activity, and it is generally thought that it is this increased quantity of protein continuously passing through the tubular cells which causes the structural changes in the tubules. Proximal tubule fluid in the dog contains an average of 5 mg./100 ml. of albumin. Assuming the same concentration in man, and a total 24-hour glomerular filtration rate of 180 litres, there is normally a tubular reabsorption of protein of less than 10 g. per day. But when the permeability of the glomerulus increases, tubular reabsorption of protein also increases. As the passage of the albumen through the tubule cell almost certainly involves some fragmentation of the molecule it is clear that an increased tubular reabsorption of albumen may be one important cause of increased protein breakdown. This is probably one reason for the recurrent finding of hypoproteinæmia in a patient with a relatively low urinary loss of protein, i.e. less than 5 g./day.

The proteins that appear in the urine are qualitatively the same as those in the circulating blood and in œdema fluid, but the proportions are different. Albumin, having a smaller molecule, is excreted in relatively much greater amounts than globulin, though small globulins account for 30–40 per cent of the proteinuria. The consequences of the loss of globulins are not clear, but globulins are known to be associated with the activity of certain enzymes and vitamins, and the carriage of some tracer metals. The loss of gamma globulins may be a factor in the well-known liability of the nephrotic patient to infection; it is also the probable explanation why immunisation procedures for poliomyelitis, influenza, tetanus or diphtheria often do not produce satisfactory levels of antibody. Plasma proteins show a diminution of all fractions except α_2 globulin, which is markedly increased. The relation between urinary excretion of protein and plasma albumin concentration is shown in Fig. 12.1. The loss of nitrogen in the urine is not only in the form of

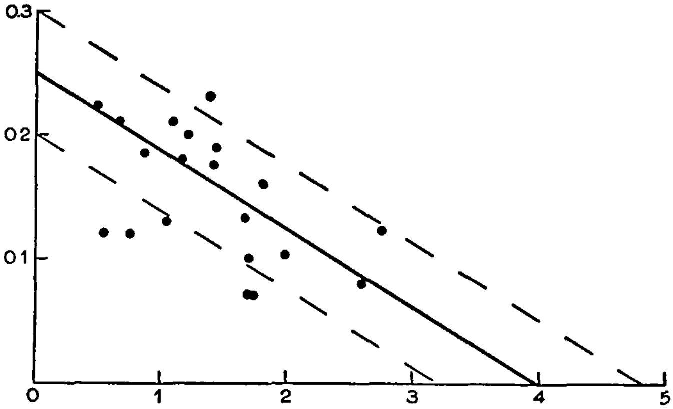

FIG. 12.1. Relation between reduced serum albumin concentration (abscissæ g./100 ml.) and daily albumin losses in urine (ordinates g./Kg. body weight). (Squire, Blainey and Hardwicke, 1957, *Brit. med. Bull.*).

protein, occasionally the loss from aminoaciduria may account for a third of the total

The quantity of protein that is excreted, if expressed in terms of its clearance (i e the amount of protein excreted per minute divided by its plasma concentration) correlates well with its molecular weight; the smaller the molecular weight, the greater the clearance In some patients the clearance of large molecular proteins, when compared to the simultaneous clearance of small molecular proteins is greater than in others Those in whom the clearance of large molecular proteins is high are defined as having a " non selective " proteinuria The semantics are unfortunate, for clearly the proteinuria cannot select anything The quantitative pattern of the proteinuria or its " selectivity " must derive from the disease process in the kidney, and in fact there is some correlation between the " selectivity " of the proteinuria and the biopsy findings As might be expected patients whose kidneys have insignificant histological changes tend to have " highly selective " proteinuria, and those in whom there are unequivocal histological abnormalities usually have " non-selective " proteinuria The " selectivity " of the proteinuria is unrelated to the total amount excreted per day, it remains unchanged during wide fluctuations in protein excretion, and it does not change as the disease progresses

With low concentrations of plasma albumin the total serum calcium is reduced, but often the concentration of ionised calcium also tends to be lower than normal, and children may develop tetany The reason for the reduction in ionised calcium is unknown, it is probably due to diminished calcium absorption Most patients also have some degree of potassium deficiency, though usually this is not sufficiently severe to cause symptoms This deficiency is due to an increased urinary loss of potassium secondary to the increased aldosterone secretion, and to a diminished dietary intake of potassium because of anorexia. Potassium deficiency is liable to become severe during treatment with resins, diuretics or steroids (see below)

All degrees of renal functional efficiency or impairment are seen with the nephrotic syndrome Some patients, particularly children, have a raised renal blood flow and glomerular filtration rate, while others have varying degrees of renal failure Because of the negative nitrogen balance the concentration of urea in the blood may be much lower than is expected from the rate of glomerular filtration, this can be very misleading if renal function is being judged only by estimations of the blood urea On the other hand, it is important to remember that patients with heavy proteinuria have particularly high creatinine to inulin clearance ratios, and that in such patients a creatinine clearance may be more than double the true glomerular filtration rate. In those patients who have a supernormal filtration rate, very low concentrations of blood urea (10–15 mg. per 100 ml.) are seen. If the deterioration of renal function is gradual, proteinuria sometimes diminishes and the œdema recedes. This is presumably because the rate of protein excretion is proportional to the filtration rate, and if this falls sufficiently the negative protein balance ceases. More often, however, as renal failure advances proteinuria and œdema remain unchanged.

Clinical Picture

The incidence of the nephrotic syndrome in relation to age and sex depends largely on its ætiology. The cases can be divided into those in whom the renal lesion is primary and those in whom it is only a feature in a more generalised disease. The primary lesions are more common in men and the majority occur under the age of 60; whereas when the lesion is a feature in a generalised disease the patients are equally distributed between the sexes.

Whatever the cause of the nephrotic syndrome the onset of *œdema* is usually gradual and fluctuating. At first there is occasional swelling of the ankles in the evening, or of the face in the morning. There may be transient attacks of more obvious œdema which rapidly disappears.

Eventually, after an interval of weeks or months, œdema persists and recovery from each exacerbation is less complete. When the condition is advanced the accumulation of fluid appears to be controlled only by the skin's limited ability to stretch. The legs and arms are unsightly lobulated balloons, shiny and pale; the abdomen protrudes both with œdema of the subcutaneous tissues and ascites; the face is spherical, bloated and disfigured particularly by circumorbital œdema, the eyes becoming pink pustular horizontal slits between distended eyelids. Pleural effusions are present, and œdema of the scrotum or vulva may produce huge swellings. The œdema is always soft and pits easily with little pressure.

As the œdema appears there is an increasing feeling of lethargy and weakness; and when there are pleural effusions there is dyspnœa. Headache is common and, for reasons which are not understood, patients with the nephrotic syndrome frequently have recurrent " colds " which, though they rarely mature beyond a sore throat and transient nasal obstruction, are often associated with an acute exacerbation of œdema and proteinuria. Bacterial infections also occur frequently and affect principally the skin, the lungs and the peritoneum. When ascites is present there may be sudden attacks of abdominal pain simulating bacterial peritonitis, but laparotomy shows only a few strands of fibrin and sterile fluid; the pain settles gradually after operation Anorexia and diarrhœa frequently occur and although œdema of the stomach and intestinal mucosa may be partly responsible for both it is clear that the anorexia is also due to the state of advanced malnutrition The latter is probably also the cause of (i) the lowered basal metabolic rate for the thyroid gland function has been found to be normal and (ii) the occasional presence of anæmia in the absence of renal failure

The combination of anorexia increased secretion of aldosterone treatment with adrenal steroids and the use of diuretics (particularly chlorothiazide) may sometimes cause severe potassium deficiency with depression of glomerular filtration rate and functional disturbances of the tubule (p 198)

Hypoproteinæmia is due to a fall in the albumin fraction and albumen concentrations below 1 g per 100 ml are sometimes seen The concentrations of the globulins however are liable to increase (except for gamma globulin) and if only total proteins are estimated may disguise the severity of the decrease in albumin concentration Nevertheless because the globulin molecules are larger and heavier than those of albumin the plasma protein osmotic pressure falls There is a rough correlation between the appearance of œdema and the plasma albumin concentration the dividing line being about 2 5—3 0 g per 100 ml

Hypercholesterolæmia is usually of the order of 400 600 mg per 100 ml although concentrations above 1 000 mg per 100 ml have been recorded During remissions of œdema or following complete recovery even when the plasma protein concentrations have returned to normal blood cholesterol values may remain raised for a matter of months and only slowly return to normal

Proteinuria usually exceeds 5 g per day and characteristically fluctuates widely from day to day being particularly sensitive to posture and exercise daily excretions of up to 50 g are sometimes seen but the usual rate is about 10–15g per day it is largely independent of the rate of urine flow The daily urine volume obviously depends on whether œdema is forming remaining unchanged or being evacuated Glycosuria is often found and microscopy shows the presence of fatty casts and doubly refractile lipid bodies

Diagnosis

The fact that a patient is suffering from a nephrotic syndrome is easy to observe its cause may be more difficult to ascertain It is suspected from the attendant circumstances and some help can be obtained from renal biopsy Often the correct diagnosis is only obtained in retrospect or at autopsy

Prognosis

The course of the nephrotic syndrome largely depends on its cause; it varies from complete recovery to death from renal failure; it may last only a few weeks or, with remissions and relapses, up to 20 years. In general, the prognosis is better in women than it is in men, and in the young rather than the elderly. Remissions of œdema may occur at any time and may last several months, with persistent proteinuria as the only evidence of disease. Sometimes such a remission may appear complete, with no protein in the urine and yet relapse takes place several years later. Renal failure, hypertensive cardiac failure with malignant hypertension and intercurrent infections are the usual causes of death. There may be periods of transient hypertension and microscopical hæmaturia, but these signs, unless they are persistent or severe, do not necessarily imply advancing destruction of the renal parenchyma. Conversely, gradual structural obliteration often takes place without proteinuria diminishing. Renal biopsy may establish the diagnosis. It is of little help in prognosis.

Treatment

The many varieties of treatment of the nephrotic syndrome are illustrated in Fig. 12.2. The conditions which give rise to the syndrome are listed at the top and the sequence of disturbed physiology which follows is shown below; the aim of the treatment can be looked upon as cutting across a chain of events at different levels.

Treatment of the Initiating Condition

This is rarely successful. Cessation of troxidone administration, or the surgical removal of a septic focus, which is giving rise to renal amyloidosis, are two exceptions. Unfortunately, the primary cause of the nephrotic syndrome is seldom amenable to treatment, and usually therapy has to be aimed at a lower or more symptomatic level. Such symptomatic treatment, however, is occasionally followed by a long-lasting remission or even complete recovery.

Treatment of the Proteinuria and Increased Aldosterone Secretion

The administration of adrenal steroids causes a rapid diminution in proteinuria and aldosterone secretion, and there is a large diuresis and loss of œdema. Presumably the diminution in proteinuria is due to some alteration in glomerular permeability, and the decrease in aldosterone secretion to inhibition of adrenal function. The following account of the use of prednisone is mainly applicable to patients suffering from a nephrotic syndrome due to glomerular nephritis. The dosage

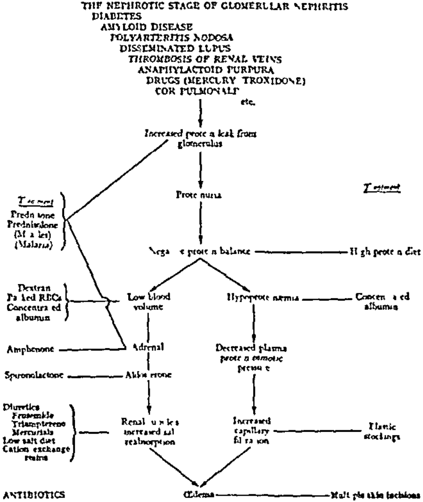

FIG. 12.2 Diseases in which the nephrotic syndrome develops: its pathological physiology and treatment.

given and the results obtained are different in children and adults; they are therefore considered separately.

Adrenal Steroid Therapy in Children It is claimed that the best response is obtained with very large doses. The aim is not only to get rid of the œdema but also to make the urine free of protein. At the onset the child is put to bed for one week. No treatment is given for this period unless a coincident *infection has to be controlled*. Very occasionally there is a spontaneous diuresis and proteinuria may disappear or diminish greatly. If proteinuria is then less than 1 g./day no further treatment is required but careful supervision should continue.

for severe proteinuria usually recurs within two years. Treatment with steroid is divided into three stages: (i) treatment of the first attack, (ii) treatment of a recurrence, and (iii) prolonged treatment.

Treatment of the first attack is planned to last 4–8 weeks. As very large doses of steroids are administered it is advisable to keep the child in hospital. Care should be taken, however, to keep him away from others with septic conditions such as eczema and tonsillitis. At first prednisone 2 mg./kg. per day (approximately) is given up to a maximum of 100 mg./day. This dose is continued for 10 days and then gradually reduced over the next 4–5 weeks. In a child weighing 30–40 lb. the following course can be given: 60 mg./day for 10 days, 40 mg./day for 10 days, 20 mg./day for 10 days and 10 mg./day for 10 days (Fig. 12.3). The possible side effects include hypertension, œdema, cardiac failure, a rising blood urea, infection, potassium depletion, or mental changes. These are rare, but nevertheless the blood pressure, weight, and jugular venous pressure should be observed each day and periodic electrolyte estimations should be made. It is also evident that the contraindications to steroid therapy are cardiac failure, severe hypertension and advanced renal failure; dyspnœa from large pleural effusions is another contraindication. Even when treatment is eventually successful there may be little change in the first seven days except for fluid retention. There is then a gradually increasing diuresis and a marked fall in proteinuria (Fig. 12.3); in the most successful cases there is also a rise in glomerular filtration rate.

At the end of the initial course of treatment injections of 10–20 units of corticotrophin are sometimes given once or twice weekly to stimulate adrenal activity in order to counteract the inhibiting effect of the prednisone. Prophylactic oral antibiotics (penicillin V or ampicillin) are given throughout the period of heavy dosage together with potassium supplements (potassium chloride 1–3 g./day), a small amount of calcium and vitamin D, and as much protein as the child will eat; no added salt is allowed. If there is a diuresis it is usually followed by an increase in weight and a phenomenal increase in appetite.

Treatment of a recurrence, or of a failure to respond to the initial course. It is usual for the condition to relapse. Treatment of a relapse consists of the administration of prednisone 2 mg./kg./day for only 4–5 days; the dose is then decreased rapidly within 2–3 weeks. If there is initial failure to respond the patient can either be given another six-week course or prolonged treatment.

The indications for *prolonged treatment* are persistent proteinuria of more than 1 g./day or repeated relapses. Either prednisone 10 mg./day every day or large intermittent doses of 20–50 mg./day (depending on body weight) are given on 3–4 consecutive days of each week In either case supplements of potassium, calcium and penicillin V are given every day of the week At this stage the children are observed as outpatients and allowed to lead as normal a life as possible It has been claimed that their growth and development remain within normal limits

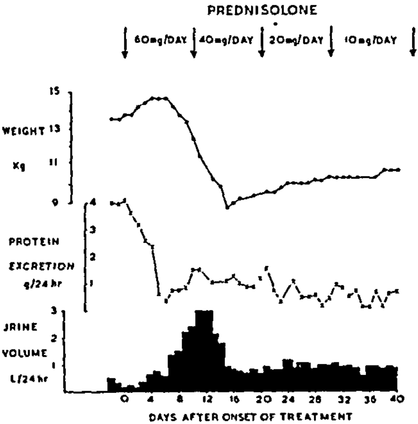

Fig 12 3 Treatment of the nephrotic syndrome with prolonged courses of adrenal steroid in a child Note the loss of weight *during the administration of very large amounts of prednisolone and the early decrease in proteinuria*

Finally, the fact that nephrotic children frequently have a remission of œdema following an accidental attack of measles has occasionally led to their being exposed to infection deliberately The results are probably due to an increased endogenous secretion of adrenal steroids but they do not seem any better than after the administration of exogenous adrenal steroids, and measles is certainly far less pleasant for the child

Adrenal Steroids in Adults. Proteinuria rarely disappears and therefore the main object of treatment is to get rid of œdema. Deterioration of renal function and hypertensive side effects are more common than in children. In addition, large doses may cause acute perforation or hæmorrhage from a peptic ulcer, acute psychosis, or reactivation of an old tuberculous lesion.

A recent Medical Research Council trial on the use of prednisone in the nephrotic syndrome due to glomerular nephritis has demonstrated that in patients with unequivocal histological abnormalities in the glomeruli, the course of the disease, and in particular the diminution in the extent of the proteinuria, is the same whether or not prednisone is given. The only advantage of prednisone administration was in that small number of patients in whom the kidneys appeared normal on light microscopy; these patients had a substantial reduction in proteinuria several months before those who did not have prednisone. Nevertheless during the course of the trial the number of deaths was greater among those patients who were given prednisone, though the difference was not statistically significant. Very rarely the administration of prednisone to a patient with a severe nephrotic syndrome, in whom renal function is rapidly deteriorating, may induce a dramatic improvement in renal function. Unfortunately it is just as likely to accelerate the rate of deterioration.

Cytotoxic Drugs. For the past few years there has been an increasing use of cytotoxic drugs such as nitrogen mustard, cyclophosphamide, azothioprine, and 6-mercaptopurine in the treatment of immunological diseases of the kidney when they are unresponsive to other forms of therapy. These drugs have been used particularly in patients in whom the disease is of recent onset and in whom there is an inexorable and fairly rapid diminution of renal function. A number of patients with a nephrotic syndrome due to glomerular nephritis have received such treatment and claims and counterclaims have been made about its efficacy. Controlled trials are badly needed.

Treatment of the Negative Protein Balance

It is imperative that the negative protein balance should be corrected, and the necessity for a high protein diet cannot be overemphasised.

The only limit to positive nitrogen balance that can be achieved by these patients is their own capacity for protein ingestion. It has been demonstrated that the rate of proteinuria is not affected by high intakes of protein and there is no evidence that renal function suffers in any way, though in patients with an initially depressed glomerular filtration rate it is important to watch the blood urea. A rising blood urea in these circumstances is of course no evidence of a further depression in filtration rate but, although a moderate rise to 40–60 mg per 100 ml is permissible, higher concentrations may be associated with symptoms of waste product retention and should be avoided Adults should, and can, eat 150–200 g of protein a day, which is not difficult if protein concentrates such as Casilan are used and salt restriction is not too severe (see below) At first anorexia is very frequent, but can *often be abolished by prednisone even if it fails to produce any other* immediate benefit It has been shown that such a diet, continued for several months, and accompanied by a large accumulating nitrogen balance may at first produce no change in plasma protein concentration or œdema, although the plasma volume is gradually increasing Eventually, when the plasma volume reaches a critical value, the œdema may rapidly recede whether or not plasma protein concentration has altered—additional evidence that the œdema in nephrotic *syndrome is more closely related to blood volume changes than to* plasma protein osmotic pressure

Treatment of the Low Blood Volume

This link in the causation of the œdema in the nephrotic syndrome can be treated directly by the intravenous administration of concentrated albumin, dextran or packed red cells Albumin is rarely given *for it is expensive to prepare and has little advantage over the other two Dextran is used most frequently It should be salt free and have* either the same or twice the osmotic pressure of normal plasma protein (5 per cent or 10 per cent solutions) The amount given is empirical but for an adult one litre of the 5 per cent solution (or 500 ml of the 10 per cent) is sufficient to produce a diuresis in many patients Packed red cells are sometimes used these should increase the blood volume for a longer period than dextran but it is doubtful whether this is so *for an increase in the red cell mass tends to be associated with a shrinking* plasma volume In addition the nephrotic's liability to pyrexial reactions is a serious disadvantage of red cell infusions unless the cells are washed with 5 per cent glucose

Blood volume expanders frequently produce a good diuresis but *shortly after* there is usually a period of relative oliguria and a rapid reaccumulation of œdema

Treatment of the Renal Tubule's Increased Salt Reabsorption

Salt and water retention can be minimised by decreasing the salt intake, or increasing the excretion of fæcal sodium by giving cation exchange resins, or it may be directly countered by increasing the urinary excretion of sodium with diuretics

Dietary Salt Content. The amount of salt in the diet should be related to the severity of the œdema and the ease with which it can be controlled with diuretics. In many long-standing cases of the nephrotic syndrome, in whom proteinuria and œdema fluctuate slowly over a period of months, the dietary salt can be adjusted according to the weight chart. When œdema is increasing rapidly it may be imperative to give a " salt-free " diet.. The ideal is to give as much salt as the patient can easily excrete; it is often an unnecessary burden to give less and it increases the difficulties of maintaining a high protein diet. One of the great advantages of the wide range of potent oral diuretics now available is that the dietary control of sodium intake need not be nearly as rigid as it used to be. If renal failure supervenes and the œdema clears it is important to remember to tell the patient to increase his intake of salt, otherwise he will develop salt deficiency which will aggravate the renal failure.

Resins. The difficulties of giving a diet low in salt and yet high in protein can be overcome to a certain extent by the administration of low-sodium protein preparations such as Casilan, and the use of ion exchange resins. A cation resin (Katonium, B.D.H.), 75 per cent in the ammonium phase and 25 per cent in the potassium phase, is given orally 15 g. four times a day, for an adult. In the small intestine the ammonium and potassium on the resin are exchanged for an equivalent amount of the patient's sodium; but much of this sodium is again exchanged for potassium in the large bowel. The net result is a negative balance of sodium and potassium, and the production of an acidosis from the absorption of ammonium. The negative sodium balance is the aim of this treatment; the negative potassium balance and acidosis are complications to avoid. The potassium loss can be countered by the oral administration of potassium citrate 3 g. per day. The kidney should be able to prevent the tendency to develop an acidosis by increasing the excretion of ammonia and free hydrogen ions (p. 63); if it is not able to do this adequately an increasing acidosis develops. Recently a cation resin in the calcium phase has been made available, this avoids the acidosis, but potassium replacements are still necessary. Resins, in line with other methods of producing a negative balance of sodium, may cause a fall in glomerular filtration rate and a rise in blood urea, if the œdema is removed too rapidly. When œdema is controlled, but heavy proteinuria continues, it is best to continue resin administration. On occasion the loss of œdema is associated with diminution or disappearance of proteinuria, a rise in glomerular filtration rate, and a return of plasma proteins to normal.

Diuretics. The guiding principle to follow is to use as many diuretics as are necessary to induce a diuresis which is not too precipitous and which does not cause a negative balance of potassium Failure to produce a diuresis with one diuretic is an indication to add a second A third, and then a fourth, or fifth may be added if necessary In order to minimise the urinary loss of potassium treatment is begun with spironolactone and triampterene Chlorothiazide can be added later and frusemide or ethacrynic acid later still (As frusemide is so effective some authorities would start with this diuretic and increase the dose until a diuresis begins) At the onset of treatment body weight must be measured each day, it is a far better guide to water balance than an "input-output" chart Plasma potassium should also be measured every other day If a diuresis still fails to occur the dosage of frusemide can be increased up to 400 mg a day If this is still unsuccessful the daily administration of all these diuretics is continued with the addition on alternate days of an intramuscular injection of a mercurial (after the preliminary administration of 1–2 g of ammonium chloride for three days) If a diuresis still does not take place the mercurial should be, stopped at the end of the first week

Once the œdema has disappeared the diuretics should be rapidly cut back in the reverse order in which they were given so that if it is found necessary to continue with diuretics the patient is discharged on spironolactone and/or triampterene Chlorothiazide and its derivatives and frusemide are dangerous drugs to use in the treatment of patients suffering from a nephrotic syndrome once they are out of hospital If diuretics are given potassium supplements must continue to be supplied but there is no certainty that such supplements will be either ingested or adequate Plasma potassium concentrations must therefore be measured from time to time Chlorothiazide or frusemide are best given to outpatients intermittently e g on two days a week or on alternate days Sometimes once a diuresis has been forced by diuretics there is a spontaneous remission with diminution in urinary protein excretion, a rise in plasma proteins and no further need for diuretics

Treatment of the Increased Capillary Filtration and Local Œdema

The increase in capillary filtration which takes place at all capillary surfaces as a result of the decreased plasma protein osmotic pressure can be minimised below the knees by wearing elastic stockings. In some subjects particularly young women who have a relatively well controlled nephrotic syndrome such a measure may enable them to go out in the evening without looking too conspicuous

Œdema fluid can be removed directly by making multiple superficial skin incisions in the legs through an antibiotic cream such as Neomycin If the patient is then kept in a sitting posture large quantities of fluid may be removed, but it is a remarkable fact that occasionally these procedures are unsuccessful for the first few days; then losses of 1–2 litres a day may occur through the same sites. This initial delay is most often seen when the accumulation of œdema has been so rapid and extensive that the legs are tense, hard and almost impossible to pit upon pressure. The danger of secondary infection of the skin during these manœuvres is considerable. For some unknown reason, if a large quantity of fluid is successfully removed in this way it may sometimes initiate the onset of a large diuresis. If ascites and pleural effusions are causing discomfort, the fluid may be removed with a needle and syringe, but otherwise this should be avoided for the protein content of such fluid is sometimes relatively high, and its removal diminishes the already depleted protein stores.

Dangers of Removing Œdema Fluid Rapidly

Aside from the dangers of an associated loss of potassium, a rapid loss of fluid, however caused, may lead to an acute reduction of blood volume. There may then be a fall in blood pressure, and a rise in blood urea. The latter is due to a fall in glomerular filtration rate and an increased protein breakdown. Potassium depletion may also occur. Nausea, thirst and faintness are useful premonitory symptoms. The blood pressure should therefore be measured twice a day and a supplement of potassium given. It is also wise to measure the hæmatocrit each day.

Treatment of the Infections

Though the use of antibiotics does not counteract a specific link in the ætiology of nephrotic œdema, their introduction in recent years has nevertheless been the main factor responsible for the longer survival of patients suffering from the nephrotic syndrome. Such patients seem particularly liable to develop infections, and in turn the infections seem to be more severe and are nearly always associated with an acute exacerbation of the nephrotic syndrome. In order to avoid infections oral penicillin is sometimes given daily as a prophylactic; alternatively the patient is given a short course of a wide-spectrum antibiotic (e.g. ampicillin) to take home, to be used at the first sign of an infection.

Synopsis of Treatment

Treatment is started with a low salt, high protein diet. Prednisone is given to children. Its use in adults now seems pointless and perhaps dangerous, though in patients with no histological renal abnormalities the administration of prednisone may be justified. If prednisone is given a remission of the proteinuria should occur within two months.

If this does not take place within that time prednisone should be discontinued

Diuretics are given in sufficient amounts to cause a diuresis If this is unsuccessful a plasma expander such as 1 litre of 10 per cent Dextran can be given during the administration of the diuretics

Ion exchange resins can also be given either as an alternative or in conjunction with diuretics Antibiotics should be given at the first sign of infection or as a daily prophylactic dose

If the œdema is painful or incapacitating even with the patient in bed and diuretics are slow to take effect the œdema may be removed with multiple skin incisions

A high protein diet cannot be used when there is evidence of renal failure

In order to be aware of the progress of events it is useful to insist on the following being measured and recorded once a day (i) body weight (ii) blood pressure (iii) fluid intake and output excluding food and fæces When there are rapid changes in weight the hæmatocrit should be measured every day and at this time plasma potassium and sodium should be measured on alternate days with plasma urea and creatinine at least once a week When the patient is stabilised these estimations can be made less and less frequently Urinary protein excretion should be measured once a week until the patient is stabilised Plasma protein concentration should be measured at least once in two weeks it is probably the best guide to progress

Long Term Results of Treatment

There seems little doubt that the duration of survival is now longer than it was and that in adults this change is due to the use of antibiotics and a high protein diet In children it is still uncertain whether the beneficial effects of prednisone have contributed to the improved survival Unfortunately there has not yet been a controlled trial of the use of steroids in children

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13

ACUTE RENAL FAILURE

Acute renal failure can be arbitrarily defined as any condition in which the daily volume of urine passed into the bladder is suddenly reduced below 400 ml.* This definition inevitably includes severe but physiologically normal oliguria, which is sometimes called "acute renal insufficiency."

Ætiology

(1) Severe functional changes without structural damage
(2) Severe functional changes with acute structural damage
(3) Functional changes of perhaps moderate severity but occurring in a patient with chronic structural damage.
(4) Acute urinary tract obstruction.

Severe Functional Changes without Structural Damage

The most important of these changes is severe but initially reversible renal vasoconstriction, the causes of which have been discussed on p. 92; they are predominantly those which cause acute circulatory insufficiency. Typical examples are the sudden reductions in blood volume which may accompany acute diarrhœa and vomiting, burns and hæmorrhage. The reduced renal blood flow which results is associated with a reduced glomerular filtration rate and thus a decreased excretion of solutes. Usually there is a simultaneous stimulation of the supra-optico-hypophyseal system and an increase in the level of circulating antidiuretic hormone. The oliguria which results is thus associated with a urine which at first is highly concentrated. Some of the most severe but rapidly reversible oliguric episodes may occur in the first two days after operation when the 24-hour urine volume may be 150 ml.

Severe Functional Changes with Acute Structural Damage

A wide variety of conditions may give rise to acute structural changes severe enough to cause acute renal failure, they are illustrated

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* This excludes a transient form of acute renal failure in which the glomerular filtration rate falls and the blood urea rises, but the urine flow remains normal. The condition has been described in association with burns and has a good prognosis.

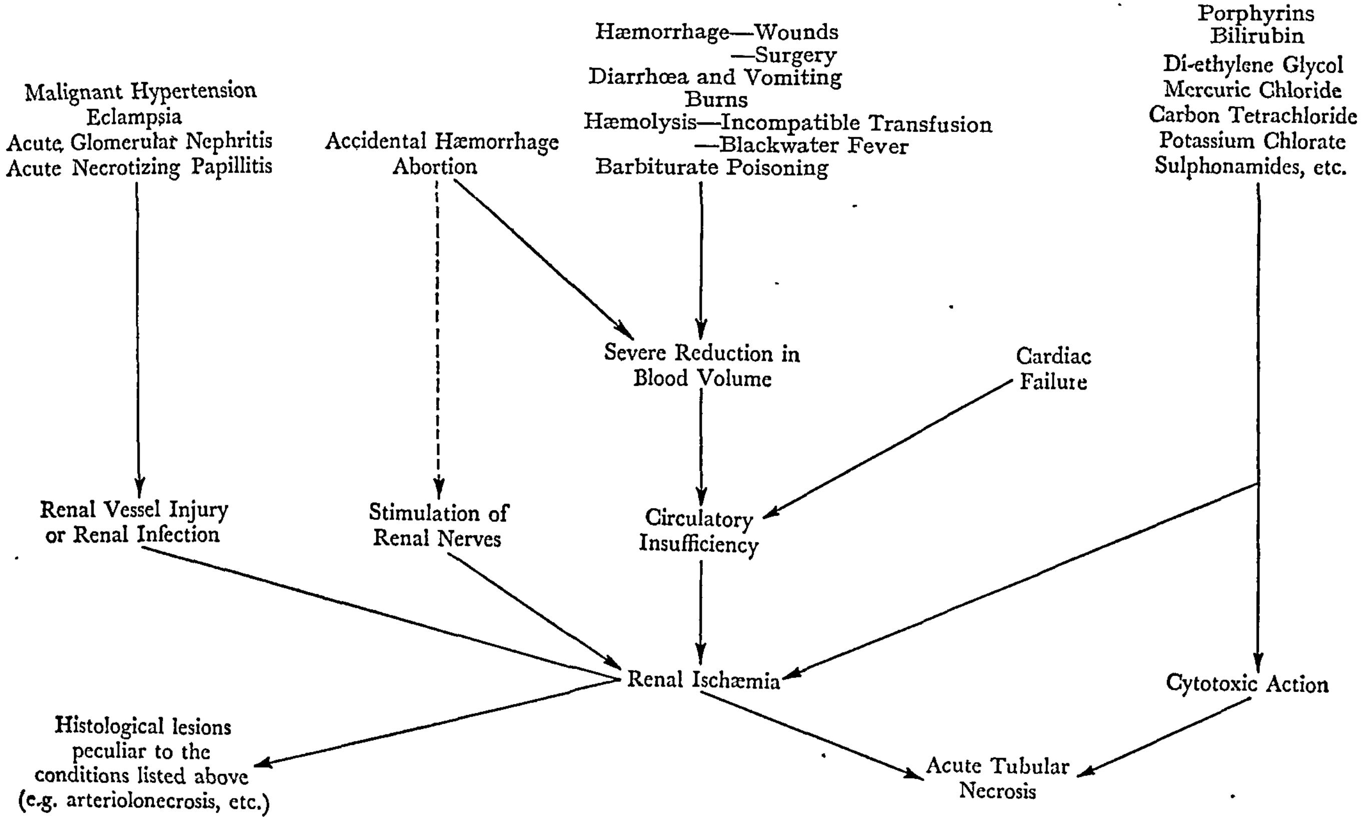


FIG. 13.1. Ætiology of acute renal failure with acute structural changes.

in Fig 13 1 They include severe forms of certain renal diseases which usually present in a less acute form, i e acute nephritis, acute pyelonephritis with acute necrotising papillitis, malignant hypertension, polyarteritis nodosa and eclampsia Numerically these are not important causes of acute renal failure The most common form of structural damage is acute tubular necrosis In the past this condition has been called "lower nephron nephrosis," 'shock kidney" and "crush syndrome"

Tubular necrosis may follow directly from the action of poisons or severe prolonged renal vasocontriction Poisons act directly by causing the death of those tubular cells which transport the substance from the blood into the lumen of the tubule, they also cause intense renal vasoconstriction and irregularly distributed focal patches of renal ischæmia, which in turn becomes the sites of ischæmic tubular necrosis Mercury, arsenic, lead, bismuth, carbon tetrachloride, potassium chlorate, propylene glycol and sulphonamides are some of the substances which have been known to cause acute tubular necrosis, for this reason they are called nephrotoxins Some endogenous substances such as porphyrins and bilirubin are also liable to produce acute tubular necrosis if present in excess quantities in the plasma

The causes of renal vasoconstriction which may produce tubular necrosis are the same as those which have been discussed above and in Section 8 Necrosis is due to the intensity and duration of renal ischæmia, i e it must be present for a matter of hours, a point of immense importance in trying to prevent the condition Abortion, multiple wounds and extensive surgery with inadequate blood replacement are the most frequent causes of tubular necrosis Though it is possible that renal vasoconstriction without a concomitant fall in blood pressure may occasionally be sufficiently intense to cause necrosis, it is clear that necrosis is more likely if there is a combination of vasoconstriction and hypotension It is not always appreciated that the more intense the vasoconstriction the higher the minimal arterial pressure necessary to keep the vessels open This is important clinically, for when there is severe renal vasoconstriction minor falls in blood pressure may be sufficient to cause a complete ischæmia

Whether a shunting of blood through the juxtamedullary glomeruli and away from the cortex ever occurs in any of these situations is not open to demonstration The meagre evidence that has been obtained in man does not support the idea, and observations made on animals suggest that if there is such a diversion, it is of little consequence compared with the severity of the total renal ischæmia with which it is associated

Acute Functional Changes Superimposed upon Chronic Structural Damage

Patients suffering from chronic renal failure due to a gradual obliteration of their nephrons may be precipitated into acute renal failure by some disturbance which, in a normal person, would cause only an insignificant change in renal function. This combination of acute functional changes and long-standing structural damage is sometimes very difficult to differentiate from acute structural damage in previously normal kidneys, particularly if the pre-existence of chronic renal disease is unknown. The differential diagnosis is based on obtaining clinical evidence of long-standing renal failure such as a history of polydipsia, polyuria, lassitude, and the presence of pigmentation and anæmia.

Acute Urinary Tract Obstruction

Bilateral pelvic or ureteric obstruction, or unilateral obstruction to a single functioning kidney can obviously cause acute renal failure. This indisputable truth is often forgotten when considering the differential diagnosis of acute renal failure. Pus, clots of blood, crystalluria, tubular debris, and retroperitoneal fibrosis (see below) can cause acute bilateral obstruction. There is also a rare condition known as calculus anuria when acute bilateral anuria results from the presence of a calculus in only one ureter.

The outstanding feature of the acute renal failure due to acute urinary tract obstruction is that the flow of urine is completely suppressed, as opposed to the low flows which are usually found with acute structural damage to the renal parenchyma. The only exception to this rule is in the acute renal failure of acute glomerular nephritis. The therapeutic implication of this fact is that if acute renal failure is associated with complete or almost complete suppression of urine, a cystoscopy should be performed and the ureters catheterised to try to relieve the obstruction; if this is unsuccessful it is necessary to release the urine above the obstruction by a nephrostomy.

Retroperitoneal fibrosis is the term applied to the presence of a thick mass of fibrous tissue in the retroperitoneal space which spreads outwards from the mid-line. Usually the cause is unknown. It can follow prolonged treatment with methysergide for migraine; and occasionally it is a response to invasion by carcinoma cells. When the fibrous mass involves both ureters it may give rise to a characteristic form of acute renal failure. The patient is usually a middle-aged man who complains of increasingly severe bouts of unremitting pain in both loins, the attacks come on suddenly and last a few hours or a day or two. A hydrocœle or œdema of the legs may be present, perhaps due to compression of veins and lymphatics Finally, during a prolonged attack of pain there is oliguria or anuria This may last a few days Then there is a profuse polyuria, perhaps only for a few hours, followed by a return of complete anuria. The concentration of blood urea fluctuates wildly with the changes in urine flow, and the urine is free of protein, a most revealing point which excludes a disturbance of the renal parenchyma as the cause of the anuria Surprisingly ureteric catheters pass up the ureters without difficulty and urine flows down the lumen of the catheters but when they are removed the anuria persists Radiographic studies may show that the ureters have been pulled inwards towards the mid line or that they are deformed in a zig zag pattern along part of their course Treatment consists in freeing the ureters and placing them laterally beyond the fibrous mass The idiopathic form of the disease *is thought to be self limiting*

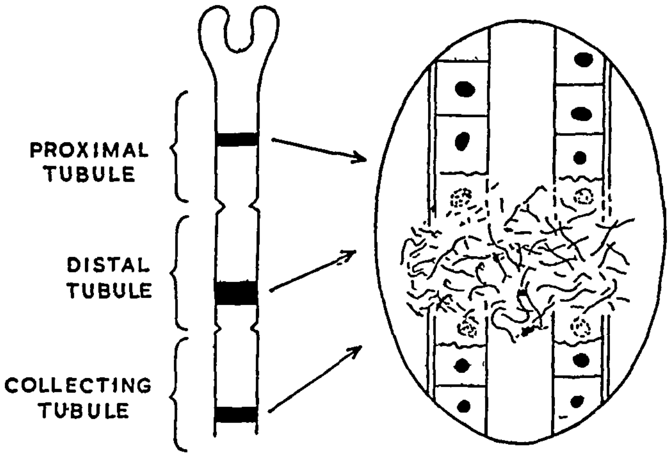
TUBULAR NECROSIS

The following sections describe the pathological findings clinical features treatment and prognosis in acute tubular necrosis. The clinical features and treatment of acute renal failure due to other causes are almost identical

Pathology of Acute Tubular Necrosis

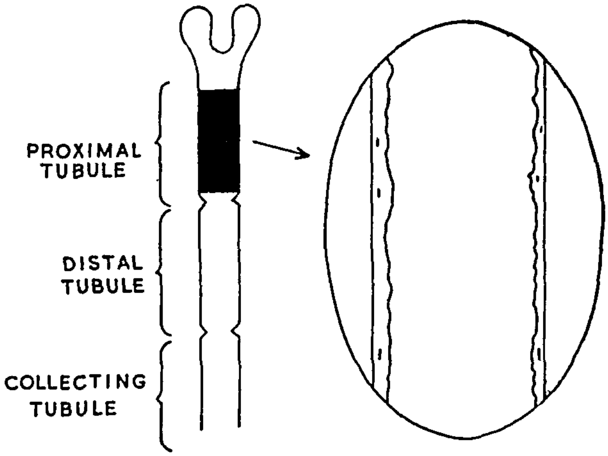
Macroscopically the kidneys do not look greatly disturbed and may often be passed as normal When the kidney is incised there is a tendency for the cortex to bulge and to look slightly pale The only unmistakable macroscopical appearances are those associated with extensive necrosis such as are found with eclampsia and accidental hæmorrhage (p 337) when the condition is called acute cortical necrosis

Microscopically the lesions are most clearly displayed in nephrons which have been microdissected *By this technique it has been possible to show that there are two distinct lesions, one is due to ischæmia and occurs in a random distribution* throughout all nephrons and in any part of the nephron down to the collecting tubule the other, which is due to nephrotoxins, affects all nephrons equally and is confined to the same part of each *proximal* tubule Each ischæmic lesion involves only a relatively short length of the nephron and consists of complete necrosis of the tubule cells and the basement membrane, thus exposing the lumen of the tubule to the renal interstitial space (Fig 13 2) The nephrotoxic lesion involves a considerable segment of each proximal tubule and consists of necrosis of tubule cells only, without involvement of basement membrane (Fig 13 3) Nephro-



ISCHAEMIC LESION OF TUBULAR NECROSIS

Fig. 13.2.



NEPHROTOXIC LESION OF TUBULAR NECROSIS

Fig. 13.3.

toxins, however, not only cause the death of those tubule cells which transport them, but in addition their presence in high concentrations causes intense renal vasoconstriction In acute tubular necrosis from nephrotoxins, therefore, both ischæmic and cytotoxic lesions are found

Ordinary histological sections of the kidney at autopsy show that the glomeruli escape injury while the even distribution of the nephrotoxic tubular lesions are easily recognised, the ischæmic lesions, however, are much more widely spaced and may not be present in a renal biopsy There are a few foci of round cell infiltration and occasionally some of the tubules are surrounded by a clear " halo "-like area which is thought to be evidence of interstitial œdema Numerous hæmcasts are seen in those cases which follow an incompatible blood transfusion or widespread muscle injury

Renal biopsy observations have shown that there is little correlation between the light microscopy changes and the functional abnormalities Indeed most biopsies show little or no light microscopy changes With the electron microscope, however, it has been possible to demonstrate that even in those specimens with no light microscopy changes there are pronounced cellular lesions in the tubules with patchy disruption of the basement membrane The glomeruli appear normal

Clinical and Biochemical Features of Acute Tubular Necrosis

Following the particular episode which has precipitated tubular necrosis and which may be defined as the onset the natural history of the disorder can be divided into three phases

(*a*) The oliguric
(*b*) The diuretic
(*c*) The postdiuretic

Oliguric Phase

The early part of the oliguric phase is *frequently unrecognised for* it oftens begins during a surgical or medical emergency In this setting, the fact that the kidneys have almost ceased to function may not immediately alarm, so great is the relief that the patient is *still* alive The daily volume of urine excreted varies, but complete cessation of urine flow does not occur with tubular necrosis At least 50–100 ml is excreted daily, it is often dark and discoloured by breakdown *products of blood, and at first may be thickened by the débris of* necrosed tubular cells, yet the specific gravity of this small volume of " concentrated "-looking urine is nearly always around 1 010, a paradox which confirms the diagnosis. *Proteinuria is always present.*

During the oliguric phase the renal blood flow is only reduced to about a third of normal whereas glomerular filtration rate is usually less than 1 per cent of normal. The cause of the continuing renal ischæmia is not known. It persists for many days after the situation which precipitated the initial renal ischæmia of the onset has been corrected. It has been suggested that renal ischæmia is caused by a rise in intrarenal pressure, for straight X-rays of the abdomen show the kidneys to be much larger than normal. This hypothesis, however, is no longer tenable, for the intrarenal pressure has been measured and found to be normal. Nor does the persistence of the renal ischæmia appear to be due to a maintained nervous vasoconstriction. The most likely explanation is that the initial ischæmia causes changes in the tubule cells from which vasoconstricting metabolites subsequently diffuse and maintain the ischæmia.

The gross discrepancy between the moderate reduction in renal blood flow and the almost complete absence of apparent glomerular filtration rate is not understood. The electron microscopy changes suggest that perhaps the true filtration rate is not greatly disturbed but that as the filtrate passes down the injured tubule most of it " leaks " back into the peritubular venous capillaries. The severe reduction in apparent glomerular filtration rate together with the tubular damage cause severe disturbances in function. Urea, creatinine, potassium, phosphate, sulphate and a considerable quantity of unidentifiable anions (which have been aptly called, for want of a better name, " anuric anions ") accumulate in the blood and extracellular fluid. There is also an accumulation of hydrogen ions with a fall in plasma *p*H and bicarbonate. The increase in the concentrations of potassium, phosphate and urea are due to their release from the breakdown of muscle protein; the rate of this release which is greatest during the first few days of the oliguric phase largely determines the course of the illness. The rise in plasma potassium is aggravated by the retention of the hydrogen ions, for these tend to be sequestered intracellularly in exchange for potassium ions which are then released into the extracellular fluid. In addition, a fall in arterial oxygen tension (e.g. with a chest infection) may also cause a rapid shift of intracellular potassium into the extracellular fluid and plasma. The danger to life is that the rising concentration of plasma potassium may cause cardiac arrest. This threat is accentuated by the rise in phosphate which lowers the plasma calcium, and, as potassium and calcium ions have opposing actions on heart muscle, the lowered calcium and the raised plasma potassium summate in their ill effects on cardiac function. There is also a rise in plasma magnesium which potentiates the harmful effects of the rise in plasma potassium. The rate of protein catabolism is greatest following injury to muscle, hæmorrhage and trauma in the young and healthy; elderly or debilitated patients break down protein at a slower rate Infection causes a brisk increase in rate In most patients protein catabolism is greater in the first two or three days On a diet containing about 100 g of carbohydrate per day the average total (endogenous + exogenous) calorie consumption is approximately 2 500 per day endogenous fat constituting the main source of energy

The other major electrolyte disturbance which occurs in the oliguric phase is a decrease in the serum concentration of sodium and chloride In the past this hypotonicity or overhydration was usually due to an attempt to relieve the oliguria by the administration of large quantities of water an intuitive therapy based on the naive principle that what goes in must come out This is a particularly easy trap to fall into for these patients are often *excessively thirsty* It has been shown however that plasma osmolality gradually falls even if the water intake is limited to an amount which is normally lost by insensible means At first there was thought to be a shift of sodium into the cells but *it now appears that the most important factor is an increase in* the extracellular water This is derived both from the intake for the insensible loss of water is below average in these patients and from metabolic water formed by the endogenous breakdown of protein and fat *a quantity which may amount to 300 ml a day* It is important to recognise the origin of this hypotonicity for its prevention and correction depends on restricting the intake of water and trying to diminish the endogenous breakdown of protein and fat *not in administering large quantities of normal or concentrated saline intravenously* this only expands the extracellular fluid space and may lead to cardiac failure ✓

Other changes evident in the blood are the development of anæmia and a leucocytosis The anæmia develops rapidly fails to progress beyond a certain severity though the oliguria may continue and often becomes more pronounced when the blood urea concentration is beginning to fall. The cause of the anæmia appears to be a combination of bone marrow depression and hæmolysis.

These many changes in the internal environment can only be diagnosed with certainty by laboratory estimations they are associated with the following rather vague clinical signs The fall in plasma *p*H results in deep regular sighing respirations which are easily recognised but the other electrolyte changes produce signs which are singularly non specific even when they are of sufficient severity to threaten the patient s life *Overhydration causes mental dullness and* headache nausea vomiting and convulsions It has also been said to cause psychosis and fever Expansion of the extracellular fluid space is recognised by a rise in jugular venous pressure œdema tachypnœa and pulmonary crepitations. The rise in plasma potassium and the fall in plasma calcium concentrations are stated to be responsible for anxiety, restlessness, paræsthesiæ and hypotension; these are particularly unreliable signs. Serial electrocardiograms are more valuable in revealing a rise in plasma potassium; initially there is " tenting " of T waves with ST segment depression, flattening of the P wave, and a lengthening of the QRS complex so that it resembles bundle branch block; at higher concentrations of potassium the E.C.G. takes on the appearance of an untidy sine wave and there may be periods of standstill and irregular rhythm. Death occurs from cardiac standstill and ventricular fibrillation. In traumatic cases, particularly those with extensive injury to muscle, the rate of rise of plasma potassium to a lethal concentration may be extremely rapid: a concentration of 6–7 mEq./l. rising to 10 Eq./ml. overnight. The rise in plasma magnesium probably produces some drowsiness and weakness. ✓

Gastro-intestinal disturbances including hiccoughs are frequent during the oliguric phase; their cause is unknown, but they become more severe as the blood urea rises; both vomiting and diarrhœa may occur and they are usually made worse by oral feeding. Occasionally there is hæmatemesis and melæna. As the oliguric phase lengthens there is a gradual clouding of consciousness, nausea and lassitude, fading into a twitching coma. These features seem to be directly due to the retention of some unidentifiable waste products, for they can be relieved by dialysis even if the concentration of blood urea and identifiable electrolytes are left uncorrected.

A rise in blood pressure is infrequent.

Delayed wound healing and hæmorrhage often occur in surgical cases. Finally, it is important to be aware that these patients are very liable to develop infections ; these are now the commonest cause of death in cases uncomplicated by severe trauma.

Diuretic Phase

This phase begins when the 24-hour urine volume reaches 1,000 ml. Together with the onset of diuresis, the renal blood flow and glomerular filtration rate gradually increase. Sometimes, however, the diuresis begins without any marked change occurring in either. At first the urine appears to be pure plasma filtrate, for the total concentration of the urine, and of each of its constituents, is identical with that of plasma. As the urine volume increases, the tubules recover some ability to reabsorb salt and concentrate urea so that the urine now contains less salt and more urea than plasma, but the total osmolar concentration still remains about the same as that of plasma, i.e.

isotonic The delay in the return of the ability to concentrate is *paralleled by a similar delay in the ability to acidify the urine*

During the first few days of the diuretic phase the patient s general condition changes markedly, there is an increased awareness, nausea and vomiting cease, and appetite returns The overall improvement is such that when blood urea estimations are found to be either unchanged or even a little higher than before the onset of diuresis, *there is often* an atmosphere of disbelief in the accuracy of the estimations Nevertheless this is the recurrent pattern of recovery and is another indication that the symptoms of renal failure are not due to the high concentra*tions of blood urea The diuretic phase may be a week old before the* blood urea begins to fall

At the height of the diuresis the daily urine volume may be very great (e g 6 l) so that whereas a few days before the patient s life was threatened by an excess of water salt and potassium it is now exposed *to the perils of dehydration salt loss and potassium lack* The cause of this extensive diuresis appears to be a combination of three mechanisms (1) An osmotic diuresis due to the high blood urea (2) tubular functional inadequacy and (3) the release of an accumulated surplus of fluid and electrolytes *Obviously if (1) and (2)* are responsible for the large diuresis dangerous electrolyte and water deficiencies may occur whereas if it is due to (3) it is to the patient s advantage The urine volume rises to a peak and then falls to normal values, the duration of the diuretic phase is roughly the same as that *of the oliguric phase*

Postdiuretic Phase

This stage develops imperceptibly from the diuretic phase and is characterised by a normal output of urine although there continues to be some *impairment of renal function Gradually renal blood flow and* glomerular filtration rate increase and the ability to concentrate the urine and other tubular functions return towards normal over a period of about one year Nevertheless follow up studies have shown that although renal function *is perfectly adequate full recovery is unusual*

TREATMENT

The first thing to do is to confirm that acute renal failure has indeed taken place and it is essential to catheterise the bladder to exclude urinary retention The next step is to decide whether the oliguria or anuria is due to urinary tract obstruction if this is considered probable *or even remotely possible* cystoscopy and ureteric catheterisation should be performed and any obstruction either dislodged or relieved by nephrostomy. This is particularly relevant when the acute renal failure follows the taking of sulphonamide or is associated with a high plasma uric acid when tubular debris and crystals can produce complete occlusion of the pelvis and ureters.

Acute tubular necrosis and other forms of acute renal failure should be treated along the following lines.

Treatment of the Onset

During the onset of acute renal failure, when there is severe renal ischæmia, but before tubular necrosis has occurred, it should be possible (except in the case of poisons) to prevent necrosis by prompt transfusion, or electrolyte and water replacement, whichever is appropriate. It is imperative that transfusions should not be withheld on the grounds that, as the patient is already suffering from acute renal failure, he should not be exposed to the risks of a mismatched transfusion. It would be as logical to refrain from throwing a lifebelt to a drowning man for fear it might hit him on the head.

It is wise to try and decide by examining a blood film whether the loss of blood has occurred in an already anæmic person, for if such a patient is transfused so that the hæmatocrit rises above its usual level, renal failure may be aggravated (p. 96), particularly if there is already some degree of chronic renal structural damage.

If a patient is seen within an hour of a transfusion reaction or the ingestion of a nephrotoxic poison it is possible that renal damage may be less extensive if a transient osmotic diuresis is induced with 500 ml. of 10 per cent mannitol intravenously in 30 min. If the renal failure is reversible the urine flow should increase by 50 per cent in the next two hours. When acute renal failure follows diarrhœa and vomiting, pyloric stenosis, etc., electrolyte and water losses should be replaced even though the presence of oliguria makes the dangers of overadministration more likely. In order to find out whether the oliguria is reversible, a litre of saline is given intravenously in one hour; if the urine flow rises to 20–30 ml./hr. or more it is reasonable to assume that the oliguria is reversible and to continue the saline administration. It has also been claimed that if the urine to plasma osmolal ratio is greater than 1·35, or the urine to plasma urea concentration ratio is greater than 6·6, the patient has a potentially rapidly reversible form of acute renal failure; whereas if it is below 1·035 or 2·14 respectively it is not immediately reversible.

Ideally the patient should never be allowed to become oligæmic long enough for severe renal ischæmia to develop. If acute renal failure does supervene it is essential that its time of onset should be determined as accurately as possible, for though rapid intravenous *therapy may be life-saving in the first few hours, 24–48 hours later it may only precipitate pulmonary œdema, cardiac failure and death*

Treatment of the Oliguric Phase

The aim of treatment during the oliguric phase is to keep the internal environment normal until the kidneys recover It is clear that this aim is limited by two factors (1) the rate at which the internal environment changes, which is mainly dependent on (*a*) the rate of catabolism, and (*b*) *the efficacy of treatment*, and (2) *the duration of* the oliguria If the internal environment changes relatively slowly, and the oliguria does not last more than two to three weeks, conservative treatment may be sufficient But if the internal changes are rapid or the oliguria prolonged then it may be imperative to supplement conservative treatment with artificial dialysis In practice it is the rate of change which is most *liable to vary*, and this in turn is *largely determined by the extent of the associated trauma and infection* When there is no trauma, e g following abortion and poisoning, the rise in blood urea and potassium is often so gradual that conservative treatment is adequate But with extensive trauma, e g gun shot wounds and road accidents deterioration is so rapid that dialysis is usually necessary This dissimilarity is not only due to probable differences in the rate of catabolism but also to the fact that traumatic cases, and *particularly war casualties are liable to have large quantities* of intracellular products released from non viable muscles which have been overlooked during débridement

Whatever means are employed to treat acute renal failure, plasma electrolytes, urea and glucose should be estimated at least once a day, the daily urine volume should be measured and its content of electrolytes and glucose estimated *The patient should be weighed each day* if at all possible, and if the patient is being treated by dietary means and not being dialysed he should lose 0 2–0 5 kg per day, for this is approximately the weight of endogenous solids which are metabolised each day

An indwelling catheter should not be placed in the bladder, for it is likely to cause a urinary infection *If the rate of urine flow is around or above 300 ml per day there will usually be spontaneous bladder voiding* once a day, if it is below this it is insufficient to influence decisions about treatment

Conservative Treatment

Control of Water Intake As soon as it is considered that the patient *is not deficient in water, the intake of water is limited to 500 ml a day*, plus a quantity equal to the amount of urine passed in the previous

24 hours. The total amount is increased in very hot weather and if there is much sweating. The amount of water required is best gauged by the weight (see above) and the effective plasma osmolality (i.e. total osmolality less the osmolality due to the urea content); if it is not possible to estimate the plasma osmolality the concentration of sodium is a less exact but useful substitute. The weight should fall gently while the plasma osmolality or sodium concentration should not change. Unfortunately, the patient's persistent thirst is no guide to his needs.

Control of Electrolyte Intake. Following any initial replacement that may be necessary the further ingestion or administration of electrolytes (except for calcium) must be prevented.

The plasma concentration of potassium should be kept below 7 mEq./l. Some authorities have suggested that this can be done by the intravenous administration of calcium gluconate and insulin (50 units per day) throughout the 24 hours. The latter, in association with a high glucose intake (see below), tends to draw the potassium into the cells and so lower plasma potassium. This is certainly true on a short-term basis, but the evidence that it is of much practical value over a prolonged period is not very strong. Resins in the sodium phase or preferably in the calcium phase are used to lower plasma potassium; the dose is 15 g. two to four times a day orally, or 60 g. as a retention enema with promulsin emulsion. The most satisfactory way to lower plasma potassium temporarily in an emergency is to give 200 ml. of molar sodium lactate intravenously in three hours. The rise in extracellular *p*H induces a compensating shift of hydrogen ions from the intracellular compartment and this in turn causes potassium to pass from the extracellular space *into* the cells.

The fall in plasma sodium and chloride should be treated by limiting the fluid intake, for, unless there is a very clear indication of sodium and chloride loss before the onset of renal failure, its administration in order to correct plasma concentrations is potentially dangerous. This also applies to any attempt to correct the acidosis by giving sodium bicarbonate or sodium lactate, for the dangers of expanding the extracellular fluid volume and causing cardiac failure are greater than any benefit gained by a transient change in *p*H.

Control of Protein, Carbohydrate and Fat Intake. It is obvious that protein intake should be controlled. Nevertheless a protein-free diet is repugnant. In addition, it has been shown that if the carbohydrate intake can be maintained at a high level (around 200 g. per day) 20–30 g. of protein per day will not influence the rate of rise of blood urea; and the patient feels much better. The additional potassium intake which this involves can easily be controlled with resins.

Carbohydrates should be free of electrolytes They are given to slow the rate of endogenous protein breakdown and minimise the rise in plasma potassium concentration (see above) 100 g of carbohydrate per day will reduce endogenous protein breakdown by 50 per cent Additional amounts up to 400 g per day will further reduce protein breakdown If the patient can be fed orally the aim is to give as much carbohydrate as can be tolerated The use of Hycal (Beecham) which contains 400 calories of carbohydrate as disaccharides and dextrose *in 180 ml of water is of enormous help, and most patients find this* palatable Anabolic steroids (Nilevar, 17-Ethyl 19 *nor* testosterone or Durabolin 19 *nor* testosterone-17β phenyl propionate) are sometimes used to delay protein breakdown particularly in obstetric cases

Fats have a protein sparing " effect and are used in combination with carbohydrates (Fat cannot safely be given intravenously and its administration by stomach tube is apt to cause diarrhœa)

ADMINISTRATION OF WATER AND CARBOHYDRATES INTRAVENOUSLY

If the patient cannot eat it is necessary to introduce water and carbohydrate requirements intravenously

PERIPHERAL VEIN An isotonic solution of glucose is one of 5 per cent if concentrations of 10–15 per cent are given into a peripheral vein, pain and thromboses are apt to occur after about 6–10 hours If the patient has many easily accessible veins an attempt can be made *to give a 15 per cent solution by changing the site of the intravenous* needle at about 8 hourly intervals In this way thrombosis may be avoided and a continuous administration maintained If the veins are " poor " then it is unwise to give a concentration greater than 10 per cent, and even with this concentration the veins are more likely to remain patent if the site of the needle is changed at least once a day Pain and swelling over the vein can sometimes be controlled by placing 10 mg of hydrocortisone in approximately each litre of infusing fluid, *and clotting in the needle can be prevented by adding 1,000 units heparin*

It is most unusual to be able to give 100 g glucose per day into a peripheral vein at these high concentrations When difficulties occur the attempt to give glucose is sacrificed to the need to keep the water intake within the bounds described above, and the concentration of the infusions are lowered

CENTRAL VEIN *Glucose concentrations as high as 50 per cent can be infused intravenously through an indwelling polythene tube placed* into the inferior vena cava via a saphenous vein for the 0 2–0·5 ml per min. of glucose solution is diluted in 2–3 litres of blood. This technique needs the least supervision and causes little overt trouble at the site of the infusion; if heparin (1,000 units per litre) is placed in the solution the tube does not become clotted; the rate of flow is always easily controlled and has no sudden fluctuations; the patient has both arms free and is not subject to recurrent needle punctures and tender veins. Nevertheless, there is one serious complication. A thrombus may form at the saphenous vein incision and spread up through the common iliac vein into the inferior vena cava. There have been some fatalities from pulmonary emboli in patients who have recovered from the renal failure.

Control of Nausea and Vomiting. These may sometimes be controlled with thiethylperazime preferably by injection.

Control of Anæmia. It is usually inadvisable to try to treat the progressive anæmia by transfusions, for the risk of inducing cardiac failure is very great.

Control of Infection. The likelihood of infection is so great that some centres now treat all patients with acute renal failure in isolation. Antibiotics are not given unless an infection develops. It must be remembered that if the antibiotic that is used is one that is usually eliminated in large amounts in the urine, e.g. streptomycin, it may be dangerous, after the initial loading dose, to give more than small maintenance doses.

Therapeutic Measures to Avoid

The frustration of seeing a patient gradually dying from acute renal failure, who may have been recently saved from death by an emergency operation, has in the past prompted the use of certain useless and dangerous measures. As they are still occasionally used they are enumerated here, so that their eventual eclipse may be hastened.

(1) The intravenous administration of large volumes of osmotic diuretics or the attempt to force a diuresis by overexpansion of the extracellular fluid space with large quantities of intravenous saline; these will almost certainly cause cardiac failure.

(2) Encouraging the patient to drink large quantities of water while giving 5 per cent glucose intravenously; this causes water intoxication, and pulmonary congestion.

(3) Renal decapsulation and paravertebral block; the trauma of the first procedure hastens the rise in blood urea, while the second may cause hypotension.

None of these measures is beneficial; some are lethal.

Dialysis

Peritoneal Dialysis Now that industry has made available a sterile disposable perforated plastic tube with a built in steel trocar and that dialysing solutions for peritoneal dialysis are also available commercially, together with disposable sterile connections peritoneal dialysis is a relatively simple and safe procedure The catheter should be placed under aseptic conditions into the peritoneal cavity in the direction of the pelvis and a strict aseptic discipline instilled into all those concerned with the dialysis There are a variety of ways the dialysis can be carried out The following has been found convenient Dialysis only takes place from 6 a.m to 10 p m —during the night the peritoneal catheter is left *in situ* but disconnected after clamping Two litres of a dialysing solution is run in and then as much more as the patient will tolerate usually not much more than another litre The fluid is then allowed to run out again immediately until two litres has been evacuated Two more litres are immediately run in and then out again In this way dialysis takes place continuously for there is always some fluid in the peritoneal cavity The number of exchanges is usually around one per hour and as the fluid is always moving through the connecting tubes the risk of clotting and fibrinous obstruction is greatly diminished Nevertheless it is wise to put 500 units of Heparin in each of the first two or three exchanges

The osmolality of commercial dialysis fluid is either near that of plasma or stronger If it is necessary to remove œdema fluid or there is some difficulty in getting the dialysis fluid to flow out of the peritoneum the stronger solution is used If possible the patient should be sat up out of bed for a few hours during the day without interrupting the dialysis for otherwise the danger of pulmonary collapse at the lung bases with subsequent infection is considerable All patients lose some protein into the dialysis fluid some lose a great deal This can be monitored to a certain extent by twice daily hæmatocrit and frequent estimations of plasma protein concentration in addition to keeping a watch on the blood pressure and the heart rate Sometimes it is worth collecting all the dialysis fluid which has been used in a day in one large container and measuring its protein content Protein loss can be made up by the intravenous administration of suitable quantities of plasma The risk of sepsis depends a great deal on how long the catheter is kept *in situ* After 36 hours the rate of infection rises steeply It is useless to place antibiotics prophylactically into the peritoneal fluid If a mid stream' sample of the fluid coming from the patient is cultured once a day an infection can be treated with the appropriate antibiotic directly into the peritoneal cavity and systemically Some patients, particularly men, suffer much discomfort during peritoneal dialysis. Considerable quantities of analgesics may have to be given and in these patients the risk of pulmonary infection is particularly great.

Haemodialysis. The main use of haemodialysis is in the treatment of patients whose kidneys have failed once and for all. Its use in acute renal failure has diminished greatly since the introduction of peritoneal dialysis.

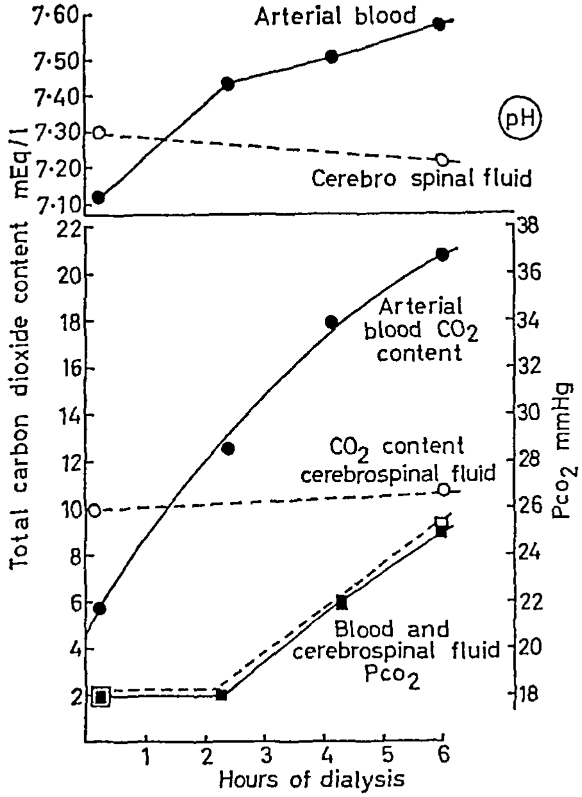


FIG. 13.4. Changes in *p*H, total CO_2 content of arterial blood and cerebrospinal fluid brought about by hæmodialysis. (Lambie, Anderton and Robson, 1964, Blackwell Scientific, Oxford).

There are many types of artificial kidneys. All of them are suitable for the treatment of acute renal failure. If such a machine is used sporadically, it is best to use one that has disposable sterile components, even if they are expensive. The purpose of an artificial kidney is to pass the patient's blood on one side of a semi-permeable cellophane type membrane while a dialysing fluid is passed on the other.

One useful dialysing fluid consists of Na^+130, K^+1, Cl^-90, acetate$^-35$, $Ca^{++}2{\cdot}5$, $Mg^{++}1$, mEq./l., glucose 200 mg./100 ml. (As acetate is metabolised to bicarbonate its use greatly simplifies the technical preparation of the dialysing fluid) The blood gradually equilibrates with the dialysing fluid and the patient should feel better It is important to note however that if this process of equilibration takes place too quickly the patient may have severe headaches vomiting fits and become unconscious This is due to the fact that during the dialysis the changes in the content of urea and bicarbonate in the brain lag behind those in the blood This causes two cerebral disturbances The first is due to the content of urea in the brain becoming higher than in the blood This causes an osmotic gradient Water diffuses into the brain and there is cerebral œdema The second is due to the brain bicarbonate rising more slowly than the blood bicarbonate The rise in blood bicarbonate is associated with a reduction in ventilation and a rise in blood P_{CO_2} towards normal As CO_2 is readily *diffusible* P_{CO_2} *in the cerebrospinal fluid rises at the same rate as in the* blood In the cerebrospinal fluid however there is now a relatively unchanged low bicarbonate but a rising P_{CO_2} with the result that the already low *p*H falls to even lower levels (Fig 13 4) These complications are avoided by not allowing the patient to become too ill before dialysis is begun by dialysing more slowly or by dialysing for short periods at frequent intervals Excess fluid is removed from the patient *by having the dialysis fluid in the artificial kidney at a negative pressure* so that water is sucked across the cellophane by ultra filtration During dialysis the patient has to be heparinised If he has recently had a surgical operation or an accident the heparin will have to be given with great care The simplest way is to give a small continuous infusion into the blood just as it leaves the patient to enter the artificial kidney The dose is adjusted so that it keeps the artificial kidney from clotting but is insufficient to cause any important change in the patient s clotting time Alternatively heparin is given in the same place but protamine is given into the blood just before it returns to the patient This is supposed to neutralise the heparin This technique is known as regional heparinisation It is a cumbersome manœuvre which has little to commend it it is rarely as satisfactory as the one mentioned above

Indications for Dialysis

It has been established that the higher the blood urea rises the worse the prognosis and if the blood urea is allowed to rise above 300 mg / 100 ml the patient may have a fatal hæmorrhage either into the pericardium or gastro-intestinal tract One important indication for *dialysis therefore is a blood urea nearing 300 mg /100 ml* As changes usually occur at a uniform rate it is a fair assumption to extrapolate into the near future from the immediate past and it is thus possible to anticipate events. Some consider that the blood urea should not be allowed to rise above 200 mg./100 ml. Another indication is a rise in plasma potassium to 7 mEq./l. despite other forms of treatment (e.g. resins). A plasma bicarbonate below 10 mEq./l. severe acidotic respiration, increasing stupor, confusion or coma are also indications but will rarely be present before the ones already mentioned.

The artificial kidney is used only in those patients in whom the rate of rise in blood urea or plasma potassium is so great that peritoneal dialysis has either been shown to be inadequate or is likely to be difficult. The first is particularly the case when acute renal failure is associated with multiple injuries in a young man, or when an infection develops; the second when there are abdominal injuries.

A tremendous advantage of dialysis, peritoneal or with an artificial kidney (particularly with a Scribner shunt in position), is that if dialyses are performed each day, dietary restrictions are unnecessary and there is no need for fluid restriction. This improves the patient's morale and his physical condition and probably reduces the length of convalescence.

Treatment of the Diuretic Phase

With conservative treatment it is vital that the strict regimen of the oliguric phase should be continued until the blood urea begins to fall. Frequently a partial recovery with a daily urine volume of about 700 ml. may progress no further for several days; it is imperative that during this time treatment should not be relaxed.

Once the diuretic phase begins the dangers to look out for and correct are water depletion, salt loss and potassium loss. It has become clear that much of the polyuria which these patients experience is often only the evacuation of excess extracellular fluid, and attempts to replace it only prolong the diuretic phase and may lead to overhydration. An exact replacement should not, therefore, be attempted unless there is evidence of need. It is more important to be guided by the patient's general condition, pulse rate, blood pressure, thirst and plasma electrolyte content than by the urine volume and its content. Intravenous therapy is stopped unless there is nausea, vomiting, confusion or coma, and the patient is encouraged to eat a high potassium, high salt diet, and given easy access to large amounts of water.

PROGNOSIS

The prognosis of acute renal failure depends on the initiating cause and its associated circumstances (e.g. multiple injuries), the severity of the renal lesion and the efficiency of treatment. It is fair to say, however, that whereas there was a mortality of about 90 per cent before the introduction of conservative treatment and artificial dialysis, it is now nearing 40 per cent. In obstetric and medical cases the mortality is rather less than 15 per cent whereas in surgical cases it is usually greater than 50 per cent. In some of the most advanced centres, however, the mortality in surgical cases has recently been brought down to between 10 and 30 per cent. 20 per cent of all deaths are due to infection, and it contributes significantly in another 60 per cent.

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14

CHRONIC RENAL FAILURE

CHRONIC renal failure consists of a persistent impairment of both glomerular and tubular function of gradual onset and of such severity *that the kidneys are no longer able to keep the internal environment normal* This definition includes mild asymptomatic functional impairment, which is sometimes called " chronic renal impairment "

Chronic renal failure follows a great number of conditions which devastate the kidney Its clinical features, however, are remarkably uniform, for usually renal failure is simply due to a deficiency of *nephrons, and a fairly fixed combination of disturbances is inevitable* It is in fact the exceptions to this recurring pattern which cause curiosity, for example, when the blood pressure has never been raised, and yet at autopsy the kidneys are found to be small and fibrous

There are certain selective disturbances of tubular function in which initially there is little or no evidence of a decline in the number of nephrons These syndromes are usually named after the particular disturbance of tubular function involved, i e familial nephrogenic diabetes insipidus, they are discussed elsewhere (p 209)

CAUSES OF CHRONIC RENAL FAILURE

1 DESTRUCTIVE DISEASES OF UNKNOWN CAUSE POSSIBLY DUE TO ABNORMAL ANTIGEN ANTIBODY REACTIONS
    Glomerular nephritis
    Polyarteritis nodosa
    Disseminated lupus erythematosus
    Subacute bacterial endocarditis.
    Anaphylactoid purpura

2 INFECTION
    Pyelonephritis
    Tuberculosis.

3 OBSTRUCTION TO THE URINARY TRACT
    Bilateral calculi
    Prostatic obstruction
    Urethral valves etc.

4 CONGENITAL LESIONS
    Polycystic disease
    Tubular abnormalities (final stages)

5. HYPERTENSION
    - Malignant.
    - Non-malignant.

6. OTHERS
    - Amyloid.
    - Gout.
    - Diabetic nephropathy.
    - Hypercalcæmia.
    - Chronic intermittent hæmoglobinuria: (i) sickle cell; (ii) nocturnal.
    - Renal vein thrombosis.
    - Myelomatosis.
    - Radiation damage.
    - Any other renal diseases which eventually destroy the nephrons, e.g. tubular changes associated with metallic cation loss.

Chronic renal failure is characterised by a wide variety of biochemical disturbances and numerous clinical signs and symptoms. It is one of the outstanding peculiarities of chronic renal failure that some of the biochemical abnormalities do not cause any symptoms, while most of the clinical abnormalities have no known biochemical cause.

The following account of chronic renal failure is divided into two parts. The first describes the biochemical abnormalities which have been identified and the clinical manifestations which they cause; the second describes the many clinical features of unknown cause.

Biochemical Features and their Clinical Manifestations

Water Metabolism

Thirst and nocturia occur frequently, polyuria is less common. The symptoms are due to a diminished capacity to concentrate the urine and to a loss of the normal diurnal rhythm of urinary excretion. Often the ability to make the urine hypotonic remains for some time after the ability to concentrate has almost disappeared; later the urine concentration remains fixed at the same osmolality as plasma, a phenomenon known as isosthenuria.

Though inability to make the urine hypertonic may be due in part to a diminished functional capacity of the nephrons which remain, it is mainly due to an increased rate of solute excretion per nephron. This is an explanation which has been advanced earlier (p. 53) but which can be elaborated here. It is evident that in chronic renal failure the total solute output remains almost unchanged, for the patient is usually in normal electrolyte and water balance, and yet nearly always there is a considerable reduction in the number of functioning nephrons. It follows, therefore, that each surviving nephron must be handling much larger quantities of solutes and water than normally This is a situation similar to that obtaining in each nephron of a dehydrated normal person who has been given a large quantity of a solute such as sucrose mannitol or urea which is then promptly excreted in the urine the rate of solute excreted per nephron increases and there is a concomitant rise in urine flow and *fall in urine concentration* i e there is an osmotic diuresis (p 52) There is now increasing evidence that the impaired ability to concentrate the urine in chronic renal failure is mainly due to an osmotic diuresis It follows that this apparent impairment is not an indication of diseased nephrons but of a deficiency of nephrons

In chronic renal failure there is frequently an increased turnover of water and the ability to dilute the urine remains normal or better than normal for a considerable time But there is diminished ability to excrete a water load rapidly This occurs before as well as after the ability to make the urine hypotonic has disappeared When it is present before it is presumably due to the diminished number of nephrons for even if each nephron forms a hypotonic urine at a normal rate there is an insufficient number to increase the total urine flow adequately This is the reason why polyuria is never gross in chronic renal failure and seldom exceeds 3–4 l /24 hours in contrast to the 8–10 litres found in diabetes insipidus or compulsive polydipsia When the kidneys can no longer form a hypotonic urine the inability to excrete a water load is easier to understand

These disturbances make patients suffering from chronic renal failure vulnerable to acute changes in water balance Diarrhœa and vomiting may quickly cause severe dehydration for the output of water and salt does not drop as sharply as in the normal conversely an impetuous intravenous administration of water (5 per cent glucose) may cause overhydration Sometimes slight nausea with a distaste for eating and drinking is sufficient to cause dehydration when a vicious circle of increasing renal failure more pronounced nausea and further dehydration then occurs

Hydrogen Ion Metabolism

On a normal diet the kidney has to excrete about 40 to 60 mEq a day of hydrogen ions to prevent the internal environment from becoming acid (p 54) In chronic renal failure there is an impaired ability to eliminate hydrogen ions which results in a systemic acidosis with a fall in plasma *p*H and bicarbonate This is due to (1) a reduced ability to excrete ammonia presumably caused by the diminished number of nephrons and (2) a reduced titratable acid excretion due to a diminished excretion of buffer phosphate which is mainly due to a diminished intake of phosphate The urine *p*H is usually below 5 0 and there is therefore no impairment in the ability to maintain a hydrogen ion gradient. Nevertheless, if the plasma bicarbonate and *p*H are raised to normal by an intravenous infusion of sodium bicarbonate or lactate and the patient observed thereafter as he returns to his original acidotic state, it is evident that the urine *p*H does not fall in a normal manner. In some patients the urine *p*H does not fall below 5·0 until the plasma bicarbonate is less than 20 mEq./l. whereas in a normal individual the urine *p*H falls below 5·0 when the plasma bicarbonate is less than 24 mEq./l. It is apparent that in chronic renal failure, therefore, the ability to acidify the urine in response to a standard rise in plasma hydrogen ion concentration is in fact below normal. This is due to the nephrons impaired ability to reabsorb bicarbonate which in turn is due to their reduced ability to secrete hydrogen ions and this stems directly from their reduced number.

The most remarkable phenomenon about hydrogen ion metabolism in chronic renal failure is that though the plasma bicarbonate and *p*H may be depressed, the plasma concentration of these two substances may remain at the same level for many weeks or months. Or in other words, though the patient can only get rid of a fraction of the hydrogen ions he is producing each day, and he is thus in positive hydrogen ion balance, *he does not become increasingly* acidotic. The probable explanation is that the hydrogen ions are being neutralised by calcium carbonate and other calcium buffers in bone.

Kussmaul respiration is the only clinical feature which is undoubtedly due to the acidosis; its severity is determined as much by the rate of fall in *p*H as by the extent of its reduction. There is also increasing evidence that at least part of the bone changes in chronic renal failure are due to the retention of hydrogen ions. In addition there is a considerable list of signs and symptoms, particularly of the alimentary and central nervous systems, which it is considered may possibly be caused by the acidosis. It is also possible, however, that the pharmacological actions of the unidentified " renal failure anions " are responsible. These clinical disturbances are discussed below.

Sodium and Potassium Metabolism

Abnormalities of electrolyte balance are unusual until the final stages of chronic renal failure. As the nephron population diminishes each remaining nephron reabsorbs less salt and secretes more potassium. This is an adjustment which is not purely passive, for salt reabsorption can be increased by dietary salt restriction or cardiac failure, and potassium excretion may exceed the amount that is filtered. Overt deficiency, or retention of either sodium or potassium, is therefore unusual. Nevertheless, patients with chronic renal failure are progressively less able to adjust to sudden changes in sodium and potassium intake In addition it is probable that a state of persistent negative sodium balance occurs more frequently than is suspected Such patients tend to excrete 2–4 l of urine a day and have a normal blood pressure, the renal lesion is often chronic pyelonephritis polycystic kidneys or long standing back pressure In these circumstances the increased liability to excrete sodium because of the osmotic diuresis per nephron is counterbalanced by an increased hormonal tubular retention of sodium which has itself been stimulated by the negative sodium balance caused by an initial nett leak of urinary sodium Very occasionally the urinary leak of sodium continues in spite of the compensatory mechanisms and the patient suffers from overt sodium deficiency Such patients have advanced chronic renal failure severe loss of renal parenchyma and adrenal hyperplasia Aldosterone secretion is increased This syndrome is sometimes known as salt losing nephritis

Disturbances of potassium balance occur even less frequently than those of sodium In contrast to sodium the tendency is for potassium retention The concentration of plasma potassium is usually raised to high normal levels or slightly above normal and during the terminal phase it is often higher A renal leak of potassium can occur but is a very rare phenomenon

Calcium Metabolism

The disturbances to calcium metabolism in chronic renal failure are multiple and largely incomprehensible Urinary calcium excretion falls to very low values (10 mg /day or less) and there is little or no calcium absorbed from the gut Calcium balance therefore is relatively normal Plasma calcium is either normal or low The cause of the low urinary excretion and gut absorption is not known nor is the occasional fall in plasma calcium understood

Patients who have suffered from chronic renal failure for several years tend to develop osteomalacia in adults (or rickets in children) osteitis fibrosa and osteosclerosis All three bony lesions are usually present at the same time though one may be more prominent The overall effect is one of decalcification It is not known whether this apparent decalcification is due to negative calcium balance or to redistribution of calcium within the bone it is probably the latter It is possible that the osteomalacia and rickets are due to a circulating substance which prevents calcium deposition in bone, such a substance has been demonstrated in the blood of patients suffering from chronic renal failure When the bone lesions become widespread there is a rise in plasma alkaline phosphatase The cause of the hyperparathyroidism (which is responsible for the osteitis fibrosa) is also unknown. It may be due to an attempt to keep plasma phosphate concentration within normal limits. It is associated with hypertrophy of the parathyroid glands and an increase in circulating parathormone. This hypertrophy is directly related to the plasma calcium so that if there is little or no hypertrophy the patient has hypocalcæmia and tends to have osteomalacia, whereas if there is considerable hypertrophy the plasma calcium is in the high normal range and the patient will have osteitis fibrosa. Osteomalacia tends to precede osteitis fibrosa.

Clinical or radiological evidence of these changes is uncommon. At first, decalcification causes no clinical symptoms. After a time it can be recognised radiologically. Later there are vague aches and pains which are frequently disregarded as "rheumatism," or arthritis. Eventually adults may be disabled by the development of the characteristic, bilateral, symmetrical lesions of osteomalacia; in children the classical deformities of rickets develop.

Severe hypocalcæmia is not uncommon, and occasionally there may be tetany. The bone lesions may be cured by the administration of calcium carbonate and vitamin D enabling the patient to lead a normal life for many years thereafter.

(It must be stressed that, though parathyroid hyperplasia occurs in chronic renal failure the level of serum calcium is usually *below* normal, that normal levels are unusual, and that levels above 12 mg. per 100 ml. do not occur unless there is an adenoma of the parathyroid. When a high serum calcium coexists with renal failure the high calcium is not the result of the failure, it is usually its cause.)

Magnesium Metabolism

Plasma magnesium and magnesium balance are normal in chronic renal failure whatever the creatinine clearance. There is reduced alimentary absorption and urinary excretion of magnesium due in part at least to the reduced intake of magnesium consequent upon increasing anorexia and medical advice to eat less protein. The ability to excrete a sudden load of magnesium, however, is severely impaired. The use of magnesium sulphate as a purgative may therefore be lethal. Some rise in plasma magnesium has also been claimed in patients taking magnesium trisilicate.

Phosphate Metabolism

As glomerular filtration rate falls, tubular reabsorption of phosphate also diminishes, and phosphate excretion remains unchanged. This is due in part to an increase in parathyroid hormone secretion which inhibits tubular reabsorption of phosphate. Plasma phosphate therefore does not rise until the creatinine clearance is approximately 10–20 ml./min., even then the rise is usually a modest one. This stability is also due in part to a fall in phosphate intake which accompanies a reduction of protein intake. Occasionally, however, particularly in patients who drink much milk, plasma phosphate may rise to more than 20 mg./100 ml. This may cause tissue calcification including acute arthritis from precipitation of calcium in the synovial fluid (pseudo-gout).

Urea Retention

The rise in blood urea is due to the diminished glomerular filtration rate. There is much evidence that urea itself is not responsible for any of the symptoms of renal failure; it has been shown that uræmic patients can be greatly improved by the use of an artificial kidney without necessarily changing the level of blood urea, and it is well known that in acute renal failure, where the blood urea rises to a plateau and then falls, the patient's general condition may be critical as the blood urea is rising, but that at an identical value a week later there may be a vast improvement.

Retention of Other Substances

It is well-established that the longer the blood urea has been raised the greater the discrepancy between the plasma concentration of non-protein nitrogen and urea. This is due to a rise in the concentrations of uric acid, creatinine, phenol derivatives, amines and other nitrogenous metabolites of protein metabolism. Plasma uric acid does not rise until the creatinine clearance is less than 20 ml./min.; very occasionally if the concentration rises above 10–15 mg./100 ml. it may precipitate an acute attack of gout. The rise in plasma creatinine is not thought to produce any symptoms. The importance of the rise in plasma creatinine is that in advanced renal failure it is a far better guide to the extent of accumulation of protein metabolites than is the level of blood urea. A blood urea of 100 mg./100 ml. may be associated with plasma creatinine levels of 3 to 20 mg./100 ml. depending mainly on the diet the patient is having, the duration of his illness and the glomerular filtration rate. A plasma creatinine of 3 mg./100 ml. is of no immediate prognostic importance, whereas with a plasma creatinine of 20 mg./100 ml. the patient is likely to die within a few days from a gastro-intestinal hæmorrhage, a hæmorrhagic pericarditis or some other calamitous complication.

It has been claimed that the increased quantity of circulating phenols is responsible for some of the features of renal failure, such as lassitude, nausea and anæmia but there is no significant correlation between the blood concentrations of phenol and any particular symptom. The rise in amines is probably of more consequence.

There is also a retention of sulphate, some unidentified anions and urochromogen. The retention of sulphate and unidentified anions together with phosphate is responsible for the fact that as the serum bicarbonate falls with the increasing retention of hydrogen ions there is no compensatory rise in plasma chloride; there may even be a fall. This is in contrast to what takes place in the tubular disorder sometimes known as " renal tubular acidosis " (p. 216) where there is hydrogen ion retention with little disturbance in glomerular filtration rate and therefore no retention of phosphates, etc. The fall in plasma bicarbonate which accompanies the accumulation of hydrogen ions is then associated with a compensatory rise in plasma chloride, i.e. hyperchloræmic acidosis.

The diminished excretion of urochromogen is one reason why the urine is pale even in subjects without polyuria; it is also claimed that the retention of urochromogen probably causes the characteristic dirty yellow pigmentation (sometimes called " earthy ") of chronic renal failure.

Anæmia

The anæmia in chronic renal failure is mainly due to a depression of bone marrow function (p. 104). Blood loss is not important except in advanced cases with a continuous slow leak from ulcers in the gastro-intestinal tract or following a hæmatemesis or melæna. In the later stages of renal failure red cell life is shortened.

If the hæmatocrit in a patient suffering from chronic renal failure and anæmia is suddenly raised by a transfusion there is a transient fall in glomerular filtration rate and rise in blood urea, due to a delay in the normal vasodilating response to a rise in hæmatocrit (p. 95). This sharp fall in glomerular filtration rate, which often takes place upon transfusing cases of renal failure, may sometimes be fatal if the presence of kidney disease is unsuspected and transfusions are continued until the hæmoglobin is normal; the blood urea rises rapidly and the patient dies of acute renal failure. Nevertheless, as acute hæmorrhage causes intense renal vasoconstriction, transfusions are occasionally inevitable; and when chronic anæmia is sufficiently severe to cause or contribute to the onset of cardiac failure, there will be an additional depression of renal function which may respond to small transfusions of packed cells.

Proteinuria and Urinary Cell Content

Proteinuria is nearly always present in chronic renal failure, but the concentration of protein in the urine is no guide to the severity of the failure, there are even reports of advanced chronic renal failure without proteinuria At first protein may appear intermittently and then only after standing in the upright posture If a nephrotic syndrome has preceded the onset of renal failure the daily protein excretion will sometimes diminish as the glomerular filtration rate falls

Granular casts and an excess number of red and white cells are also found (p 33) The characteristic though uncommon finding of advanced renal failure is the appearance of broad casts, evidence of dilated nephrons

Clinical Features of Unknown Cause

Gastro-intestinal

The tongue in renal failure is classically described as being brown and dry Though it is true that such an appearance is frequently seen it is a change which is by no means confined to those suffering from renal failure It may occur in any patient who breathes through his mouth, particularly if he has pyorrhœa and bleeding gums, and it is almost inevitable if he is also dehydrated and hyperpnœic A foul taste in the mouth is a frequent complaint in chronic renal failure and the patient may notice a taste of ammonia, particularly on waking due to the decomposition of urea

The breath may smell of urine This is characteristic of advanced renal failure and is sometimes the first sign to be noticed It is not present in every case, and often when it has been confidently identified it turns out that the smell has originated from urine in the trousers of a patient with prostatic difficulties, whose blood urea is normal A person with a normal blood urea but suffering from severe pyorrhœa may also have a uræmic breath

Hiccough is almost invariably present in advanced chronic renal failure and may cause much fatigue and distress, it appears in episodic attacks of varying length and is usually brought on by eating and drinking

Anorexia, nausea and vomiting are almost always present They are often the most prominent and, occasionally, the only symptoms, they are responsible, in part, for the extensive loss of weight of chronic renal failure. Nausea and retching may be particularly pronounced in the early morning All severities of vomiting occur, from two to three times a day to an almost continuous series of painful retches, and both small and large quantities of fluid are brought up Dehydration follows more or less rapidly and is due to a combination of circumstances which reinforce each other; there is a distaste for fluids by mouth, combined with a loss of fluid from the stomach and an inability to concentrate the urine, so that urine flow tends to remain high. Dehydration in turn causes a further reduction in renal blood flow and glomerular filtration rate, and these aggravate the renal failure so that anorexia, nausea and vomiting become worse.

Sometimes the first complaint is one of fullness after meals with or without vomiting. Such patients are often suspected of having some local stomach condition such as a peptic ulcer. This diagnosis is even more likely to be considered if the patient first appears with a severe gastro-intestinal hæmorrhage. Hæmatemesis and malæna are most frequent towards the terminal phase of renal failure and should not therefore cause any confusion, for by this time the presence of renal failure is usually known. Nevertheless, it is remarkable how often renal failure may progress to an advanced state before the patient decides, or is forced by circumstances, to see a doctor. Gastro intestinal hæmorrhages are due to a combination of increased capillary fragility and local ulceration; the latter is particularly pronounced in the large bowel. The effect of hæmorrhage in chronic renal failure is extremely serious, for the accompanying renal vasoconstriction and fall in blood pressure lower the glomerular filtration rate even further and cause a precipitous rise in blood urea. When the hæmorrhage is from the gastro-intestinal tract, some of the blood is digested and absorbed so that there is a large ingestion of protein at a time of diminishing renal function.

Constipation is common, but occasionally severe diarrhœa may occur and may quickly cause death from dehydration.

Neurological

Cerebral. Headache, lassitude, languor and a feeling of muscular weakness are all present during the final stages of renal failure; they may occur much earlier. Frequently there are recurrent bouts of depression and apathy, but the tenacity with which most patients will try and overcome their disabilities is remarkable. They may become torpid during the day and yet not be able to sleep during the night, when instead they are restless and confused. Finally, there is loss of consciousness, but often even at this late stage there may be short lucid intervals; not infrequently the patient retains a complete understanding of what is happening to him right up to a few hours before death.

Epileptic convulsions in chronic renal failure may be due either to sudden increases in blood pressure in patients with established hypertension, or they may occur without any change in blood pressure. Both types are very rare; the first is called hypertensive encephalopathy; the other has no particular designation. The latter variety is seen mainly in young adults in whom the fits may be the only complaint and yet the blood urea is extraordinarily high e g 400 mg per 100 ml

In advanced renal failure muscle twitches are often seen, they are caused by anterior horn cell discharges of unknown cause and are unrelated to any apparent change in calcium metabolism though they can often be relieved by the intravenous administration of calcium

Peripheral Nerves Uræmic polyneuropathy is a rare syndrome which has recently emerged into certain prominence in patients inadequately treated with intermittent hæmodialysis (p 186) It is due to a destruction of the myelin sheath and axons of medullated fibres in the peripheral nerves The onset may be associated with painful burning feet followed by a progressive numbness and weakness The feet and legs are affected more than the arms and the distal segments more than the proximal Eventually ataxia is prominent with a wide based steppage gait Sometimes there may be no subjective sensory disturbances The cause is unknown It is not due to a deficiency of vitamin B_1 It is cured by increasing the duration of dialysis so that it is presumably due to the retention of some injurious substance

Cardiovascular

Hypertensive Vascular Disease Hypertension and chronic renal failure are closely related (p 107) and though hypertension may cause renal failure the reverse is more common The blood pressure frequently rises in chronic renal failure but its rise may produce few symptoms when they occur they are due to widespread vascular changes or cardiac failure

The vascular lesions may be acute or chronic. They can nearly always be observed on inspection of the ocular fundus where they produce certain characteristic disturbances of the retinal arteries and of the retina The acute changes (i e those found in malignant hypertension) produce an appearance called *hypertensive retinopathy* while the chronic changes are called *arteriosclerotic retinopathy*

Hypertensive retinopathy is distinguished primarily by the presence of papillœdema which at first may be unilateral There are also flame shaped or blotchy hæmorrhages fanning out from the optic disc and multiple areas of white discoloration known as exudates These have indefinite margins and are of uneven size and colour, a lack of precision and uniformity which has caused them to be called soft exudates They consist of collections of œdema fluid Sometimes the œdematous retina lies in folds radiating from the macula towards the optic disc an appearance referred to as a macular star Soft exudates and hæmorrhages may precede the development of papillœdema

In arteriosclerotic retinopathy the retinal arteries become tortuous and narrow, either irregularly or evenly along their whole length. They characteristically cross the veins at right angles, as opposed to the more usual oblique direction, and at these crossings the veins appear to be compressed by the artery; this appearance is known as arterio-venous nipping. It is due to an accumulation of connective tissue between the artery and the vein, so that in fact the vein, as it approaches the artery, is not compressed but obscured. Exudates are also seen, but they are " hard " as opposed to those seen with the acute vascular changes. They are small and compact, they have definite, sharp margins, and are of a dense yellowish-white colour. Eventually they are found in clusters particularly spreading out radially from the macula; another form of macular star. As chronic vascular changes frequently precede by several years the onset of the acute changes it is not unusual to find arteriosclerotic and hypertensive retinopathy combined.

Hypertensive retinopathy may cause varying degrees of visual impairment, depending on the degree of papillœdema and the site and extent of the hæmorrhages and exudates (particularly if the macula has been involved). The striking clinical finding, however, is that often both fundi may be severely affected without the patient being aware of any change in vision; with arteriosclerotic retinopathy visual symptoms are even less frequent.

The changes which hypertensive vascular disease may produce upon renal structure and function have been described on p. 112. When they are superimposed upon chronic renal disease, they will intensify the severity of the renal failure. If cardiac failure occurs there is an additional sharp deterioration in renal function. With malignant hypertension cardiac failure is often one of the presenting clinical features. There are acute attacks of paroxysmal nocturnal and postural dyspnœa, and eventually œdema with a permanently raised venous pressure. Deterioration in renal function is due to (1) the reversible renal vasoconstriction associated with cardiac failure, and (2) the local vascular lesions.

The onset of *acute* vascular changes in the kidney is revealed not only by the sudden change in renal function but also by the onset of hæmaturia and increased proteinuria. The deterioration in renal function due to the vascular changes associated with malignant hypertension is partially reversible if it has not progressed too far before treatment is started. How far the functional changes produced by chronic vascular changes are reversible is uncertain.

Pericarditis. An aseptic, fibrinous pericarditis often develops in the terminal phase of chronic renal failure. Its cause is unknown. It may be painless or excruciatingly painful Occasionally it may be associated with a large bloody effusion

Hæmatological

Anæmia leucocytosis and a raised erythrocyte sedimentation rate are all common features of chronic renal failure The cause of the anæmia has been described above The mechanisms of the other two are unknown

Respiratory

The deep sighing respirations of acidosis have already been mentioned The other respiratory complications of renal failure are (1) uræmic lung and (2) infection

Uræmic lung is a radiological diagnosis It consists of dense bilateral opacities radiating from the hilum into the lung substance while the upper and lower zones and the outer rim of the middle zones are clear These appearances are usually due to left heart failure but there is a group of patients in whom they are associated with a normal pulmonary artery pressure when they are presumably due to increased transudation from abnormal capillaries

Pneumonia is frequently the immediate cause of death it usually develops only when the patient is already moribund It is not improbable that the deep respirations of acidosis and the rapid respiration of left heart failure prevent the bronchioles from becoming blocked and the lungs from collapsing the usual preliminaries to pneumonia in semiconscious patients

Cutaneous

The characteristic pigmentation of renal failure together with the anæmia give patients suffering from chronic renal failure a pale dirty beige colour The eyelids tend to be slightly swollen and an expression of tiredness and depression is common *It is not known why the eyelids should be swollen but it is not due to retention of salt and water in the extracellular space*

In advanced renal failure there may be purpura usually preceded and accompanied by bleeding gums this is probably due to some capillary disturbance the platelet count remains normal

Pruritus is common and there may also be a variety of unspecific rashes including erythema vesicles and urticaria The skin is often very dry because of dehydration recurrent boils carbuncles and slowly healing scratches and abrasions are not infrequent

Treatment of Chronic Renal Failure

Treatment of chronic renal failure can be divided into two stages. The first consists of conservative measures which are designed to delay the progressive deterioration of renal function or mitigate its consequences. The second begins when these measures are no longer able to keep the patient at work and leading a normal life. At this point the patient has entered the stage of terminal renal failure when the only effective treatment is either intermittent dialysis or transplantation.

Clearly it is of the utmost importance to try and identify the primary cause of the renal failure, for in some instances, e.g. when it is due to infection of the renal parenchyma, obstruction of the urinary tract, or malignant hypertension, it may be possible to treat the immediate cause of failure, and so prevent any further deterioration of function; often it may even be possible to obtain a large measure of improvement. Unfortunately, in most instances the cause of chronic renal failure is not treatable, for it is either unknown, or structurally irreversible, as with chronic glomerular nephritis, or congenital polycystic kidneys.

Conservative Treatment

This may be very rewarding, for often much of the disturbance in renal function is reversible, having been caused by a vicious circle in which the disturbed renal function causes a change in the internal environment, which in turn leads to a further depression in renal function, e.g. renal failure → polyuria and nausea → dehydration → renal vasoconstriction → diminished glomerular filtration rate.

Conservative treatment consists mainly in preventing or correcting disturbances of water and electrolyte balance, controlling the rise in arterial pressure, and delaying the retention of the end products of protein metabolism.

Treatment of Biochemical Abnormalities

Water. It has been pointed out on p. 26 that in normal man the amount of urea excreted in the urine is proportional to the urine flow up to urine flows of 2 ml./min. (i.e. approximately 3 l./24 hr.); in chronic renal failure this relationship is still present and even appears to hold at greater urine flows. There is also evidence that a high turnover of water increases glomerular filtration rate. A large fluid intake and high urine flow will therefore not only prevent dehydration but will also ensure a maximal rate of urea excretion. Unfortunately in many patients thirst is not a sufficient stimulus to prevent their becoming dehydrated. Some patients, particularly women, habitually drink very little, and they must be advised to drink rather more than they are accustomed to, i e an extra three to four glasses of water a day In the average case it is sufficient to point out that the fluid intake should be generous The dangers of overhydration are minimal when water is being taken by mouth

When severe dehydration has occurred through nausea, vomiting or diarrhoea it should be corrected immediately by the intravenous administration of 5 per cent glucose, or half strength saline.

Electrolyte and Acid Base Balance The acidosis of chronic renal failure rarely causes any generalised symptoms The main reason for trying to correct it is to prevent the bone changes which a persistent and accumulating retention of hydrogen ions may cause In addition the administration of the sodium ion (if sodium bicarbonate is given) will greatly improve the wellbeing of those patients who may be in negative sodium balance

Acidosis can be controlled by the oral administration of sodium bicarbonate 3–9 g /day. Calcium carbonate 6–10 g /day can also be given though *it is less effective than sodium bicarbonate in raising plasma bicarbonate, it is useful, however, when the intake of sodium must be restricted as in heart failure or severe hypertension* Calcium carbonate also gives rise to a positive calcium balance which may also be of value When there is a sudden fall in plasma bicarbonate due to a sudden deterioration of renal function and it is thought necessary to treat the acidosis promptly, it may be corrected by the intravenous administration of sodium bicarbonate The speed of infusion, however, should be carefully controlled for otherwise there may be a sharp fall in the *p*H of the cerebro-spinal fluid with giddiness, nausea vomiting and disturbances of consciousness This is due to the same mechanism as that which causes a similar syndrome during a rapid dialysis for acute renal failure (p 160)

It should be remembered that sometimes ammonium chloride is given to test renal function, or to increase the diuretic effect of mercurial injections, in chronic renal failure this may precipitate or aggravate a state of acidosis

Retention *of sodium chloride is associated either with cardiac failure or the nephrotic syndrome, the treatment of the former is discussed on* p 181 *Treatment of the nephrotic syndrome when combined with renal failure is awkward and difficult A high protein diet must not be given, for it will raise the blood urea as will the* administration of prednisone The only procedures which are likely to be useful are the administration of diuretics and a low salt diet

Gross sodium chloride deficiency arising from excess urinary loss is rare in chronic renal failure, its treatment is dealt with on p 195 Minor sodium chloride deficiency due to excess sweating, mild diarrhoea, or glycosuria can be avoided by ensuring that the salt intake is liberal. It is always dangerous to restrict the salt intake of patients suffering from chronic renal failure, particularly if the blood pressure is normal, e.g. the use of a salt-free diet in the treatment of migraine. The ability to conserve salt is limited and a contraction of the extracellular fluid space may develop insidiously with all its complications, particularly renal vasoconstriction, *hypotension* and deterioration in renal function.

Potassium retention is unusual in chronic renal failure, and only occurs as a terminal event. It may respond to 15–20 g. of cation exchange resin in the sodium or calcium phase, given orally three times a day; potassium deficiency from excess urinary loss is also most unusual; its treatment is discussed on p. 198.

Calcium Metabolism. Osteomalacia, rickets and osteitis fibrosa can be cured by the administration of large quantities of vitamin D and calcium carbonate. The dose of vitamin D depends on the patient's response, but may have to be of the order of 3 mg. of calciferol eight-hourly.

The patient's symptoms are relieved within a week or two and radiological improvement is detectable within a few months. It is interesting that eventually the bones are radiologically denser than normal. The administration of calciferol with milk as the calcium supplement, as opposed to calcium carbonate, may raise the plasma phosphate and cause metastatic calcification and arthritis. If plasma phosphate rises it can be quickly depressed by the administration of 50–100 ml. of aluminium hydroxide gel per day and decreasing the dietary intake of phosphate. It is important to control the administration of vitamin D by estimating the concentration of serum calcium and alkaline phosphatase at frequent intervals. If the dosage is excessive there will be hypercalcæmia, if it is insufficient the alkaline phosphatase will remain raised. In some patients in whom the principal disturbance is osteitis fibrosa and who have a high normal plasma calcium, the calcium absorption caused by the administration of vitamin D and calcium carbonate immediately causes hypercalcæmia. It may then be necessary to remove some of the hypertrophied parathyroid tissue surgically.

Treatment of Hypertensive Vascular Disease

Malignant Hypertension. If the patient has malignant hypertension the blood pressure must be lowered immediately; otherwise the prognosis is less than two years. The success of treatment depends not only on the ability of the hypertensive drug to lower the blood pressure but also on the ability of the kidneys to function at the lower pressure (p. 99); the latter probably depends on the extent of irreversible arteriolar narrowing present before treatment is begun If lowering the blood pressure raises the blood urea the position is hopeless To avoid this complication it is probably better to lower the blood pressure gently over a matter of days in order to allow the renal circulation time to adapt to the lower pressure

The response to treatment, and survival is slightly better in those patients whose *malignant hypertension and impaired renal function is superimposed upon chronic renal disease*

Non-Malignant Hypertension. *Both in man and animals* there is a close association between hypertension and sclerotic vascular lesions In man the progress of renal damage from " non malignant ' hypertension is so slow that it rarely causes death from renal failure It is generally agreed, however, that renal function in chronic renal disease deteriorates more rapidly once there is a pronounced rise in blood pressure Accordingly it is considered reasonable and justifiable to try and lower even a symptomless hypertension if there is any cause to believe that there is underlying renal disease

The blood pressure can often be brought under control most effectively by combining the administration of hypotensive drugs with a low intake of sodium In chronic renal failure this causes a substantial sodium depletion more quickly than in a normal person and may lower the blood pressure but it may also induce a rapid deterioration of renal function Nevertheless, if one is alert and is closely monitoring the patient's progress it is worth attempting As soon as the blood pressure is under control the intake of sodium must be increased towards normal, the intake then being adjusted according to the patient's weight, blood pressure and renal function

Cardiac Failure At first, cardiac failure responds rapidly to bed rest, morphia, digitalis and a low sodium diet, diuretics are also used, but with more restraint than is usual in patients who have heart *failure unassociated with renal failure To prevent recurrences it is usually necessary to treat the hypertension (see above) which is the principal cause of the heart's failure*

In advanced renal failure, cardiac failure may be most resistant to treatment Rest in bed aggravates the dyspnœa so that it is better to sit the patient up in an armchair or a cardiac bed, it is difficult to avoid digitalis overdosage or to induce a saline diuresis, lowering the blood pressure is now almost certain to depress renal function to lethal levels as will any attempt to correct the anæmia

Treatment of Anæmia and Blood Loss

The anæmia of chronic renal failure is unresponsive to almost all forms of therapy except the transfusion of red cells. Nevertheless, there is little point in giving blood, unless there has been a recent haemorrhage. Transfusions inhibit the bone marrow's production of red cells so that the packed cell volume usually quickly returns to its previous level. It is customary to give iron preparations by mouth, though they are rarely effective.

Hæmorrhage must be treated as rapidly as possible with transfusions of whole blood. The dangers to renal function of under- and overtransfusion have already been mentioned.

Treatment of Superimposed Infection

In patients with chronic renal failure an attack of acute pyelonephritis, however mild, may cause a severe reduction in renal function. Any suspicion of renal infection should therefore be treated promptly with antibiotics. The important point to remember about these infections is that clinically they may not be obvious; they should therefore be kept in mind when there is an otherwise unexplained deterioration of renal function.

Infections elsewhere than in the kidney may also cause a deterioration of renal function but, with the exception of subacute bacterial endocarditis, these usually present fewer diagnostic difficulties.

Treatment of Hiccough

There are many methods of treating hiccough, including the inhalation of carbon dioxide, and the administration of chlorpromazine or mepyramine (Anthisan). The latter can be given in doses of 100 mg. four-hourly by mouth or by injection; it is sometimes useful when all else has failed. Occasionally a drop of oil of peppermint on a piece of sugar is sufficient to stop an attack.

Treatment of Nausea and Vomiting

The best treatment is the 20 g. protein diet mentioned below. Sometimes at the beginning it may be useful to perform one or two peritoneal dialyses to obtain an initial return of appetite. If this is unsuccessful the patient should be placed on intermittent dialysis or transplantation. In those patients who cannot eat the 20 g. protein diet and for whom intermittent dialysis or transplantation are not available nausea and vomiting can be best controlled by the administration of thiethylperazine or chlorpromazine. In the terminal stages chlorpromazine not only abolishes nausea and vomiting, but it calms the patient's anxiety. It also reduces the quantity of drugs needed to control the other two distressing features of terminal renal failure, dyspnœa, and physical and mental restlessness. Morphia is useful for dyspnœa, and in combination with chlorpromazine will not cause nausea and vomiting If restlessness and distress are not sufficiently controlled by chlorpromazine and morphia, paraldehyde is given either as an enema or by intramuscular injection This induces a comforting drowsiness Barbiturates are also useful in this respect, but they are less reliable than paraldehyde, sometimes causing an unhappy, confused drowsiness which aggravates the restlessness

Treatment of Retention of Waste Products of Protein Metabolism

The concentration of urea in the blood is controlled by the rate of protein intake and the glomerular filtration rate In chronic renal failure glomerular filtration rate falls, the blood urea rises and there is a concomitant deterioration in the patient's general condition As it *is clear that urea is not directly responsible for this change, presumably it is due to the accumulation of other end products of protein metabolism For this reason alone the patient will feel better, and may survive longer, if protein intake is limited*

Another, more debatable reason has been advanced for reducing protein intake It has been pointed out that in chronic renal failure each remaining nephron has to excrete an increased quantity of solutes and that urea forms a large controllable fraction of this total It has been suggested that the increased 'work' that each nephron must therefore perform may accelerate its eventual destruction It has been shown that in animals the renal lesions of senescence can be accelerated by a high protein diet and that following unilateral nephrectomy and the removal of large portions of the other kidney, structural changes in the remaining renal tissue can be hastened by the administration of large quantities of protein If these results are applicable to man then once renal failure has been diagnosed, protein intake should be reduced, whatever the initial concentration of blood urea Generally, however, the therapeutic implications of these experiments are not accepted, and protein intake is regulated only to control symptoms

Low Protein Diet It is unusual to limit protein ingestion until the blood urea concentration rises above 70–100 mg per 100 ml, for symptoms of waste product retention rarely appear below these levels. A fall in blood urea can sometimes be obtained without severe dietary difficulty or negative nitrogen balance, by reducing the daily protein intake to slightly more than 0·5 g per kg body weight (approximately 40 gm protein diet (p 384)) together with a high calory intake

If the blood urea continues to rise and particularly if anorexia and nausea develop the diet is then changed to a daily intake of 20 g of protein with at least 3 000 calories (p 384) A positive nitrogen balance can be maintained if there is at least 0·22 g./kg./day of high quality protein such as meat, or eggs to supply essential amino acids. For those patients with *normal* blood pressures it is important to ensure that the diet contains a normal content of sodium (e.g. at least 100 mEq./day. This is difficult with such a diet and it may be necessary to give oral supplements of a slow release sodium chloride supplement (capsules of salt cause nausea, vomiting and epigastric pain). The improvement in general well-being caused by this diet is remarkable. Appetite returns, mental faculties become more clear and lassitude diminishes. The blood urea falls to 100 mg./100 ml. or lower with glomerular filtration rates of 3 to 6 ml./min. The patients who do best are those with normal blood pressures, and they are the ones who tend to have large urine volumes. Patients with severe hypertension do badly. Progress is assessed by measuring plasma creatinine. Whatever the level of blood urea and however satisfactory the patient's clinical condition the outlook is poor if the plasma creatinine continues to rise. Often the plasma creatinine rises while the blood urea remains unchanged. When the plasma creatinine reaches 15 mg./100 ml. the patient is liable to die very soon from a hæmorrhage. At this level of plasma creatinine, and as it rises further, the patient's physical well-being begins to be marred by an increasing sense of anxiety, restlessness and insomnia. Nevertheless, this diet has certainly done much to diminish the protracted periods of severe ill-health which used to accompany the last stages of renal failure.

A transitory fall in blood urea can sometimes be induced by the administration of anabolic steroids. This effect, however, is least noticeable in patients on a low intake of protein, and if there has been much loss of weight.

Intermittent Dialysis and Transplantation

It is important to decide whether a patient is to be treated with intermittent dialysis or transplantation *before* he is moribund. The optimum time to place a patient on intermittent dialysis is when conservative treatment has either failed to enable the patient to stay at work or failed to prevent the plasma creatinine rising to around 13–15 mg./100 ml.

Intermittent Dialysis

This can be either intermittent peritoneal dialysis or hæmodialysis.

Intermittent Peritoneal Dialysis. This is a useful (if painful) holding manœuvre for about two to three months. A fresh disposable catheter is inserted into the peritoneal cavity two or three times a week.

Dialysis is performed for about 18 hr each time the catheter being removed at the end of each dialysis Automatic cycling devices have been introduced to simplify the procedure and some patients have been treated at home Nevertheless because of the complications mentioned earlier (p 159) few patients can be maintained on peritoneal dialysis for longer than six months Dietary restrictions are similar to those for intermittent hæmodialysis (see below) Those who do best are middle aged women with normal blood pressures who are passing large volumes of urine

Intermittent Hæmodialysis An arterio-venous shunt is established into one of the patient s limbs with a teflon silastic catheter or by side to side anastomosis of the radial artery to a nearby vein This allows repeated quick atraumatic access to the patient s arterial and venous circulation at all times Dialyses are performed on a Seattle modification of the Kiil kidney using a cuprophane membrane The advantage of this kidney is that it only holds 125–170 ml of blood It therefore does not need priming with blood before each dialysis and it has such a low resistance to blood flow that the patient s own arterial pressure is sufficient to circulate the blood through the kidney This avoids the use of blood pumps

If the patient is treated in a communal centre he is dialysed for 14 hr on two nights a week if he is being dialysed at home he is dialysed for 10 hours on three nights a week Dietary restrictions depend to a large extent on the daily urine volume residual renal function and the blood pressure The aim is to keep the weight gain between dialyses down to less than 1 5 kg and to keep the blood pressure normal Water and sodium intake are therefore regulated accordingly Sodium intake has to be regulated more strictly at the beginning of treatment than after a year or two it is usually limited to 20–50 mEq /day Potassium intake is limited to around 50 mEq /day and protein intake to between 40 and 70 g /day depending on the patient s weight The calory intake is raised to the maximum possible e g 3 000 calories or more

The bone marrow depression of chronic renal failure is relieved to a certain extent by intermittent hæmodialysis and most patients will keep packed cell volumes of 20 to 25 per cent without transfusion Hypertension is brought under control by reducing the patient s weight by 1 or 2 kg at each dialysis by ultrafiltration As much as 20 kg may have to be removed before the blood pressure is controlled

Complications There are two main types those that concern the shunt and those that concern the patient s milieu intern

The silastic teflon shunt may clot or the site of the shunt may become infected Clotting of the shunt is now much less of a problem since the introduction of anticoagulants to all patients who tend to clot their shunts, the prothrombin time need only be increased by 50 per cent. Infections are more serious and nearly always cause a loss of the shunt. They can be kept to a minimum (around one per 2 " patient years ") by scrupulous attention to asepsis and good care of the cannula site. The average life of a shunt should be at least nine months. The other complications of dialysis include peripheral neuropathy, metastatic calcification and calcium " gout ", decalcification of bones and peptic ulcers. These are principally due either to underdialysis or insufficient attention to the calcium content of the bath which should be 6 mg./100 ml., i.e. the concentration of filtrable calcium in plasma.

Survival. If intermittent hæmodialysis is properly carried out, the patient is well, sexually active and at work; 80–90 per cent are alive at the end of two years. If intermittent hæmodialysis is incompetently performed, particularly if its main purpose is to provide a " pool " of patients for transplantation the patients are less well, their lives are unhappy, and survival is less certain.

The Future. It is probable that intermittent hæmodialysis will become increasingly available. Some countries are tending to develop many large communal centres in which up to 50 or more patients may be dialysed simultaneously. In others it is proposed to have a few relatively small centres in which up to 10 patients only are dialysed simultaneously. These centres will be used to instruct an increasing number of doctors and nurses. The further expansion of the service being by means of home dialysis. When home dialysis machines become simpler and more reliable and particularly when the manufacturers are prepared to give a daily emergency service, home dialysis will rapidly expand. The reluctance of industry to become seriously involved in dialysis has probably been the greatest cause for the slow expansion of intermittent hæmodialysis.

Renal Transplantation. A kidney is removed from either a living donor or a corpse and transplanted into the patient suffering from terminal renal failure. The use of living donors is now considered less and less justifiable unless the patient and the donor are identical twins.

The functional efficiency of the transplanted kidney mainly depends on the compatibility of the tissue antigens of the corpse and the patient. The greater the incompatibility the quicker the patient's immunological mechanisms cause the kidney to be rejected. If they are completely compatible, as in identical twins, there will be no rejection.

The surgical technique involved in renal transplantation is relatively simple. The prospective patient has usually been kept alive by intermittent hæmodialysis beforehand. It is customary to remove the patient's own kidneys before or during the transplantation operation.

The principal difficulty is to bring the kidney and the patient together rapidly after the donor dies. A variety of techniques have been evolved to prevent the kidney from deteriorating in the interval but none can do so for more than a few hours. Immunological rejection of the transplanted kidney may be particularly violent a few days after the transplant operation. Rejection is suppressed by the administration of cytotoxic drugs such as azathioprine, 6 mercaptopurine and actinomycine, and also by using the immunological suppressive action of prednisone. It is usually necessary to continue two or more of these drugs in small doses indefinitely. In rare instances the transplanted kidney has eventually appeared to be accepted by the recipient and the administration of cytotoxic drugs and prednisone has been discontinued.

Complications. The complications of renal transplantation are mainly those which affect the transplanted kidney or its ureter, and those which are due to the drugs used to suppress rejection. Apart from infection and infarction the kidney may suffer any of five pathological processes. Acute tubular necrosis may occur. It appears immediately after the operation and is due to deterioration of the kidney before it is transplanted. Acute rejection may develop a few days later and is characterised by a heavy infiltration of mononuclear cells, plasma cells and eosinophils together with acute destruction of the renal parenchyma. If these acute hazards are avoided three other more gradual changes may occur, a slowly progressive interstitial nephritis, an occlusive arteritis, or changes which appear to be identical to those of chronic glomerular nephritis. Necrosis of the ureter at its insertion into the bladder is a relatively common problem which again appears to be due to a rejection phenomenon.

The complications which stem from the use of cytotoxic drugs are those of immunological and bone marrow suppression including fulminating infections with agranulocytosis, and multiple hæmorrhages from thrombocytopœnia. The patient may die of infections with various fungi or viruses which are rarely pathogenic in other circumstances. The administration of prednisone often causes the classical florid facies of Cushing's disease, it may also reactivate pulmonary tuberculosis, a peptic ulcer or cause an acute psychosis.

Survival. In 1966 the centres with the best results had approximately 60 per cent of their patients alive at the end of two years. The difference between the results obtained with kidneys taken from living donors did not appear to be significantly different from the results obtained with kidneys taken from corpses. Among those patients who were alive at the end of two years there were some with kidneys in the last phase of rejection who were unable to work.

The Future. It is obvious that once it becomes possible to identify tissue antigens, renal transplantation will become increasingly successful. The main difficulty in countries such as England and the United States of America will be to obtain a sufficient supply of normal kidneys from suitable corpses. Either the law will have to be changed so that kidneys can be removed from a corpse without it being necessary to obtain the consent of the relatives as is the existing custom in France, or a publicity campaign, similar to that which has been so successful in obtaining eye donors, will have to be launched. It will also be necessary to improve methods of storing kidneys.

The Relationship Between Intermittent and Hæmodialysis and Transplantation. Both should be developed for both are needed. It is most unlikely that in the next few years the demand will be met by either, or both together.

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15

THE ACUTE NEPHRITIC SYNDROME

THE acute nephritic syndrome consists of a sudden onset of oliguria, œdema, hypertension, raised jugular venous pressure and proteinuria, due to an abrupt generalised disturbance which involves the kidneys. In some patients one or more of these features may be absent, e.g. there may be no proteinuria.

The acute nephritic syndrome may develop in a previously normal person, it may occur as a transient complication in chronic renal failure, or be superimposed upon a nephrotic syndrome. It may also precede chronic renal failure, the nephrotic syndrome or acute renal failure. It is seen in a variety of diseases which affect the kidney, including all stages of glomerular nephritis, polyarteritis nodosa, anaphylactoid purpura, disseminated lupus erythematosus, and following irradiation of the kidneys (Fig. 15.1). It occurs most commonly in acute glomerular nephritis.

Structural Changes in the Kidneys

The glomeruli usually show cellular hyperplasia, mainly endothelial with widening of the capillary walls, and varying degrees of inflammatory cell reaction. In the more severe cases the tubules show focal areas of degeneration associated with clumps of inflammatory cells. On occasion an acute nephritic syndrome may occur without histological lesions.

Functional Changes

Proteinuria is rarely greater than 2–5 g. per day, and there is an increased urinary excretion of red cells, granular casts and blood casts. As the urine is usually acid the hæmoglobin in the red cells changes to acid hæmatin and, if there is sufficient blood, the urine becomes dark brown. Lesser quantities of blood cause a smoky turbulence when the urine is gently shaken; the presence of blood is confirmed microscopically. These urinary changes are directly related to the histological changes in the glomerular tufts, for when there is no proteinuria the glomeruli are normal.

Glomerular filtration rate is often reduced, but it is remarkable how frequently the blood urea concentration remains within normal limits, if the patient previously had normal kidneys In those with pre-existing renal disease and long-standing impairment of filtration rate, the further depression in filtration rate associated with the acute nephritic syndrome causes a substantial rise in blood urea. The renal blood flow is usually unaffected except in the most severe

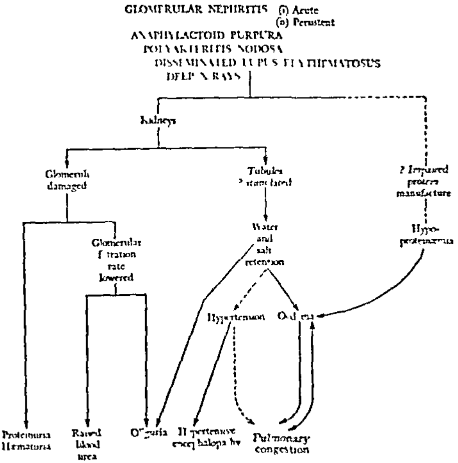

FIG 15 1 Diseases in which the acute nephritic syndrome may develop and *some of the physiological disturbances which take place*

cases and in those with pre-existing renal disease; when the blood flow is reduced the decrease is always proportionately less than that of the glomerular filtration rate, i e there is a fall in filtration fraction

The ability to concentrate the urine varies with the degree of tubular damage; *if the syndrome complicates established chronic* renal failure there is nearly always a complete inability to concentrate

Salt and water retention is due to an excessive tubular reabsorption of salt, of unknown cause, and is mainly responsible for the œdema. The acute salt and water retention causes an increase in weight, an expanded plasma volume, and a fall in packed cell volume, hæmoglobin and plasma proteins. The salt and water retention is also responsible for the concomitant hypertension, rise in jugular venous pressure, cardiac enlargement and pulmonary venous congestion. It has been shown that in spite of these appearances of " heart failure, " the arterio-venous oxygen difference is normal both at rest and during severe exercise. There is therefore no evidence that the heart is failing as a pump. In addition, no unequivocal histological lesions in the heart muscle have ever been described. It seems that the retention of sodium and water and the rise in blood volume is associated with redistribution of blood centrally into the heart and lungs. The mechanism responsible for this phenomenon is unknown; it may be due to an increase in peripheral venous tone.

Hypoproteinæmia is usual and occasionally it is severe; it must then also contribute to the formation of œdema. The cause of the hypoproteinæmia is obscure. The retention of water may cause a mild dilution of plasma proteins, and it is possible that on very rare occasions a particularly heavy proteinuria may be partly responsible. Nevertheless, the acute fall in plasma albumin to below 1·0 g. per 100 ml. which occasionally occurs in patients with acute *anuria* from glomerular nephritis makes it extremely likely that, at least in these cases, there has been a considerable diminution in protein production. It is possible, therefore, that a diminshed protein production is a contributory factor in the mild hypoproteinæmia which is usually found in the acute nephritic syndrome. When there is severe hypoproteinæmia there is also a marked rise in serum cholesterol.

The rise in jugular venous pressure, cardiac enlargement and pulmonary venous congestion occurs in nearly all patients. Paroxysmal attacks of postural and nocturnal dyspnœa are rare, but milder degrees of dyspnœa are relatively common. The heart rate is often either unchanged or slower than normal. In fact this combination of raised jugular venous pressure and bradycardia can be one of the most diagnostic features of the acute nephritic syndrome.

The sudden onset of hypertension probably causes the bradycardia. The extent of the rise in blood pressure varies a great deal and often it is so small that it is only noticed retrospectively, particularly in children. The cause of the rise in blood pressure appears to be related to the salt and water retention, for it does not occur without œdema and a gain in weight; it also seems to be related to the histological changes in the glomeruli, though occasionally the blood pressure may be normal in the presence of extensive glomerular proliferation and exudative inflammation

Clinical Features

At the onset the patient notices that the face hands or feet are swelling or that the urine has changed colour to dark brown or red Very occasionally dyspnœa may be the presenting symptom, this is more likely in children or when there is pre-existing renal disease There are few other complaints though upon direct questioning it may be possible to obtain a history of a recent gain in weight oliguria and lassitude *Severe pain in the back often occurs with polyarteritis* nodosa and an ache in the loins seems to be a genuine feature of acute glomerular nephritis Feverish symptoms and the extent of the rise in temperature vary with the cause of the syndrome Children often present with loss of appetite and pallor

Progress depends a great deal on the disease with which the syndrome is associated but in the majority of cases the signs and symptoms *subside within 7–14 days There is a brisk diuresis and hypertension and œdema quickly disappear* When the syndrome is superimposed upon pre existing renal disease recovery may be much slower and some additional impairment of renal function may be permanent In patients with previously normal kidneys recovery is often complete particularly with acute glomerular nephritis Death during the acute phase of the syndrome is unusual but may be caused by pulmonary œdema acute *renal failure or hypertensive encephalopathy*

Treatment

Occasionally it may be possible to influence directly the disease which has precipitated the acute nephritic syndrome for instance the use of adrenal steroids in polyarteritis nodosa Otherwise treatment is symptomatic and is aimed at preventing or *minimising* the effects of pulmonary œdema acute renal failure and hypertensive encephalopathy until there is a spontaneous recovery

It is convenient to keep a day to-day chart of the fluid intake urinary output blood pressure weight and 24 hour urinary protein excretion 24 hour creatinine clearance should be estimated once a week

Pulmonary Œdema and Congestion In most patients there is no *necessity to treat this by any means other than the salt and water* restriction mentioned above The dyspnœa of the onset usually settles after a few hours bed rest, but if it increases it may be necessary to use digitalis and morphia and to sit the patient up in an armchair or cardiac bed throughout the 24 hours Hypotensive drugs are useful when there is a considerable rise in blood pressure During a paroxysm of acute pulmonary œdema with deepening cyanosis, hexamethonium 25 mg. intravenously may be life-saving. On general principles the use of diuretics is not advised and, in any case, they rarely succeed in producing a diuresis in an acute nephritic syndrome.

Renal Failure. As renal failure is usually minimal and of short duration its treatment is not difficult. During the oliguric phase the patient is placed on a salt- and protein-free diet, and the daily fluid intake is limited to a volume equal to the urine passed in the previous 24 hours, plus 500 ml. to replace insensible loss. As soon as a diuresis starts, and the glomerular filtration rate returns to normal, these restrictions are relaxed.

In the rare cases when there is acute renal failure with either complete anuria or a daily urine output below 400 ml. with a specific gravity around 1·010, treatment is as described for acute renal failure from any other cause, except that measures taken to avoid acute pulmonary congestion have to be more carefully observed than usual.

Hypertensive Encephalopathy. This exceedingly rare complication responds to the intravenous administration of barbiturates (sodium amylobarbitone or thiopentone). After the initial injection it is usually sufficient to continue sedation with large intermittent doses of barbiturates by mouth. If these measures are not sufficient the fits can be controlled by lowering the blood pressure with methonium drugs, given either intravenously or intramuscularly.

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16

RENAL FUNCTION AND LOSS OF METALLIC CATIONS

THERE are two important links between loss of metallic cations and renal function (1) Renal failure may be responsible for a negative balance of sodium potassium calcium or magnesium because they are lost in excessive amounts in the urine (2) a negative balance of sodium potassium or an excessive urinary excretion of calcium may cause renal failure while a negative balance of magnesium causes changes in renal function

SODIUM

Sodium Deficiency *due to* Renal Failure

The following renal diseases may sometimes be responsible for an excess urinary loss of sodium

1. Chronic pyelonephritis
2. Advanced chronic renal failure
3. During recovery from acute tubular necrosis.
4. Renal disease of moderate severity combined with dietary salt restriction

Sodium Deficiency *as a cause of* Renal Failure

The following conditions may occasionally cause such a loss of sodium that its deficiency contributes materially to the onset of renal failure

1. Severe diarrhoea and vomiting (e g pyloric stenosis)
2. Post-operative gastric suction without replacement
3. Intestinal and biliary fistulæ
4. Diabetes.
5. Acute pathological processes involving the brain
6. Hypo-adrenalism (Addison s disease)
7. Diuretics

Clinical Features of Sodium, Chloride and Water Deficiency

Sodium loss is usually accompanied by chloride and water loss the deficiency of the chloride is usually proportional to that of sodium but the negative balance of water is usually smaller, for the patient often continues to drink. The extracellular fluid, therefore, tends to become hypotonic, and there is a transfer of water into the cells. The eventual signs and symptoms of sodium deficiency are thus a combination of those due to intracellular overhydration, and decreased extracellular fluid volume. The former gives rise to cerebral and the latter to cardiovascular abnormalities.

The patient is drowsy, restless, apathetic, and sometimes unco-operative. There is thirst (despite the hypotonic plasma), headache, anorexia, nausea and postural giddiness; vomiting may occur and there is a liability to faint on standing; eventually muscle and abdominal cramps develop and the patient may pass into a muttering delirium. There is loss of weight, the face is haggard and the eyes sunken, the skin is clammy and cold and, on pinching, it tends to remain raised; the superficial veins are thin and constricted; the tongue is dry and the eyeballs soft; the pulse is rapid and both the mean arterial and the pulse pressures are decreased. The circulating hæmoglobin concentration is raised, but plasma sodium and chloride are lowered. If salt deficiency is not corrected the patient may die rapidly from peripheral circulatory failure.

It must be emphasised, however, that there may be a considerable loss of salt before there is much clinical evidence of deficiency. But even a subclinical deficiency is sufficient to cause renal vasoconstriction with a fall in renal blood flow and glomerular filtration rate, and an increase in blood urea. When salt deficiency is secondary to renal failure the urinary specific gravity is around 1·010 and the urine contains some sodium; whereas if the kidneys were previously healthy, tubular function remains normal, the specific gravity will at first be greater than 1·020 and the urine will contain no sodium. Proteinuria is nearly always present.

Ætiology and Diagnosis

Sodium, Chloride and Water Deficiency ***due to*** *Renal Failure.* Chronic pyelonephritis is the most common renal disease to cause florid salt and water deficiency particularly during and immediately after an acute flare-up of infection. It has also been reported with chronic glomerular nephritis and polycystic disease; the syndrome is sometimes known as " salt losing nephritis " (p. 169). Very rarely sodium deficiency may also occur during the recovery stage of acute tubular necrosis (p. 152). The chronic renal diseases which cause sodium deficiency may give rise to serious diagnostic difficulties but the salt and water loss following acute tubular necrosis should be anticipated.

Sodium, Chloride and Water Deficiency ***as a cause of*** *Renal Failure.* Salt and water deficiency following post-operative gastric suction, intestinal and biliary fistulæ should also be anticipated the onset of renal failure in these conditions is often an indication of mismanagement

The risk of precipitating renal failure by giving low salt diets to patients suffering from renal disease has been mentioned earlier (p 180)

Renal failure from loss of water and salt caused by diarrhœa and vomiting or diabetic ketosis does not usually present any diagnostic difficulties But when it complicates acute cerebral conditions it may easily be overlooked

The greatest diagnostic difficulty is in differentiating the sodium chloride deficiency and renal failure of Addison s disease from sodium chloride deficiency due to chronic renal disease In both the deficiency is due to a urinary leak of salt and in both there may be nausea weakness loss of weight pigmentation hypotension and a raised plasma potassium In an emergency the two conditions can be distinguished by the fact that the administration of hydrocortisone and 9α flourohydrocortisone to patients with renal disease has little effect on the high rate of urinary salt excretion while recovery occurs rapidly upon giving large amounts of salt and water When there is more leisure to make the diagnosis it will be found that in sodium chloride deficiency due to renal disease the concentration of plasma cortisol is normal or raised while the urinary excretion of ketogenic and ketosteroids is normal and that of aldosterone is raised

Treatment

This consists simply in the rapid intravenous administration of large amounts of isotonic saline preferably with sodium bicarbonate in a proportion of 2 to 1 Isotonic saline contains 150 mEq /l of sodium and 150 mEq /l of chloride whereas the extracellular fluid contains 140 mEq /l of sodium but only 100 mEq /l of chloride the administration of one litre of isotonic sodium bicarbonate (150 mEq of sodium) for every two of saline ensures that sodium and chloride are given in physiological proportions If acute renal failure has already occurred the rate of infusion must be more moderate for great care is needed to prevent the onset of pulmonary oedema it is also essential that sodium bicarbonate be given for the kidneys are unable to excrete the excess chloride in the sodium chloride solutions

Sodium and Chloride Deficiency with Excess Water Intake

Occasionally patients who are suffering from salt deficiency and oliguria are inadvertently given water (5 per cent glucose) intravenously They may not excrete this water and they then develop acute overhydration with nausea vomiting and mental confusion

Treatment consists in the intravenous administration of about 300 ml. of hypertonic (3 per cent) saline.

POTASSIUM

Potassium Deficiency *due to* Renal Failure

The following renal diseases may sometimes cause an excess urinary loss of potassium.

1. Chronic glomerular nephritis.
2. Chronic pyelonephritis.
3. Polyarteritis nodosa.
4. During recovery from acute tubular necrosis.
5. Renal tubular acidosis (p. 216).
6. Renal artery stenosis (p. 116).

Potassium Deficiency *as a cause of* Renal Failure

The following conditions may cause such a loss of potassium that its deficiency contributes materially to the onset of renal failure:

1. Prolonged vomiting, e.g. pyloric obstruction.
2. Prolonged diarrhœa, e.g. small bowel insufficiency, excess use of purgatives or enemata, pancreatic adenomata, and villous tumours of the large bowel.
3. Post-operative gastric suction.
4. Intestinal and biliary fistulæ.
5. Uncontrolled diabetes.
6. Injudicious use of ion exchange resins.
7. Aldosteronism.
8. Diuretics.

Clinical Features of Potassium Deficiency

Until potassium deficiency is advanced its signs and symptoms are vague and indefinite. The outstanding and characteristic feature of advanced potassium deficiency is the development of muscular weakness which progresses to paralysis and death from respiratory failure. Otherwise there may be thirst, irritability, nausea, confusion and paralytic ileus. The physical signs are apathy, loss of reflexes, loss of motor power, tetany, gasping respirations and occasionally irregularity of the heart rate. The severity and localisation of the effects of potassium deficiency are influenced to a certain extent by the patient's age. The elderly appear to be more susceptible and tend to have predominantly renal and cardiac complications, whereas the young are less susceptible and tend to have the muscular changes. If the potassium loss is due to renal disease the presence of which is unsuspected, many of these features may at first be thought to be due to hysteria.

A certain diagnosis of low serum potassium can only be made by direct estimation, though some information can be obtained from an electrocardiograph which shows flattened T waves, often with prominent U waves and ST depression. Though the serum concentration of potassium is sometimes of value when the loss of body potassium is severe, it is sometimes misleading, particularly when rapid shifts of potassium are taking place from one fluid compartment to another. The cells may then be severely deficient in potassium though the plasma concentrations are normal or even high. In relatively steady conditions a serum potassium of 3 mEq./l. implies a potassium deficit of about 200–300 mEq. When potassium deficiency is primary and renal failure its consequence, the plasma bicarbonate is usually raised, but when potassium deficiency is due to renal disease the plasma bicarbonate may be reduced because of the impaired ability to secrete hydrogen ions and ammonia which accompanies chronic renal failure. Alkalosis is initially caused by the diminished amount of potassium in the tubule cells. Sodium reabsorption is then associated with a rather greater secretion of hydrogen than potassium ions from the tubule cells into the tubule lumen. This in turn generates larger quantities of bicarbonate than normal and the plasma bicarbonate rises. A larger load of bicarbonate thus has to be filtered at the glomerulus and a larger reabsorption of bicarbonate results. This active process of bicarbonate reabsorption automatically reduces the passive reabsorption of chloride. Chloride excretion therefore rises. In the final stage there is therefore, a combination of potassium and chloride deficiency and bicarbonate retention. Alkalosis is also due in part to a shift of hydrogen ions into the intracellular fluid, in exchange for intracellular potassium which is released into the extracellular fluid to prevent its concentration from falling to a lethal level. Sodium ions also cross into the intracellular fluid in exchange for potassium so that in pure potassium deficiency there is an overall intracellular sodium retention. Chronic potassium deficiency is often associated with œdema without evidence of heart failure or rise in jugular venous pressure.

Presumably the renal failure which follows potassium deficiency is due to lack of potassium within the tubule cells, for both functional and histological changes are mainly found in the tubules. The ability to concentrate the urine is lost at an early stage though the ability to dilute remains for a considerable time, occasionally the urine may remain at a fixed concentration which is hypotonic to plasma. Polyuria and particularly nocturia are therefore distinctive features of renal failure associated with potassium deficiency. In some patients this is aggravated by a complete inversion of the normal diurnal rhythm

Following the administration of ammonium chloride, the ability to form a highly acid urine, and to excrete hydrogen ions at a normal rate is impaired though the ability to excrete ammonium remains normal or raised for a considerable time. Changes in glomerular filtration rate follow and are less severe than the tubular changes. The rise in blood urea is also due in part to an increased permeability of the proximal tubule to urea. Nearly always there is a trace of protein in the urine.

The most characteristic histological change found in potassium deficiency in man is extensive vacuolation of the cells of the proximal tubule; this change is rapidly reversible after potassium administration. The more advanced appearances are those of interstitial nephritis and are not reversible. In animals there are extensive changes in the collecting ducts which have not yet been identified in man.

Ætiology and Diagnosis

Potassium Deficiency ***due to*** *Renal Failure.* This rare phenomenon is characterised by the continued excretion of substantial amounts of potassium in the urine despite depleted body potassium and low plasma potassium. The renal disease responsible for such a deficiency is easy to diagnose when it occurs during recovery from acute tubular necrosis, but it is more difficult to distinguish when it is due to chronic glomerular nephritis, chronic pyelonephritis, polyarteritis nodosa or a selective defect of tubular function. A distinguishing feature of polyarteritis nodosa is pyrexia, which occurs in all cases, even when the only sites overtly involved are the kidneys.

The early stages of potassium deficiency due to a selective error of tubular function (Renal tubular acidosis) may sometimes be differentiated from chronic destructive renal disease such as glomerular nephritis by the fact that with the former the impairment in glomerular filtration rate is moderate, and the ability to produce a highly acid urine and to excrete ammonia in response to ammonium chloride is grossly abnormal (p. 65). With chronic destructive lesions, though there is also an impaired ability to excrete ammonia, glomerular filtration rate is severely reduced and the ability to excrete a highly acid urine appears normal until potassium deficiency itself impairs the ability to excrete an acid urine (see above).

Potassium Deficiency ***as a cause of*** *Renal Failure.* This syndrome is more frequent than its converse and its cause is usually more easily diagnosed. When potassium deficiency causes renal failure the loss of potassium is nearly always from the alimentary tract. Vomiting, gastric suction, diarrhœa, intestinal fistulæ and the misuse of ion exchange resins are easily identifiable causes of excessive loss of potassium. Long-continued use of purgatives and small bowel insufficiency may be more obscure, but there is usually some looseness of the bowels. In all these conditions the urine contains only minimal amounts of potassium (p. 73) and except with ion exchange resins, the plasma bicarbonate is raised (p. 57). This combination of renal failure, low plasma potassium and low urinary excretion of potassium, proves that the renal failure is indeed due to ***extrarenal*** loss of potassium.

Very occasionally when severe potassium deficiency has been present for some time, the severity of the renal damage which results may impair the reabsorption of potassium. Urinary potassium excretion then rises in spite of the hypokalæmia and it may now be difficult to distinguish whether the renal failure is due to the potassium deficiency or vice versa. Compulsive, depressed, post-menopausal women, who obtain satisfaction and relief by secretly taking large quantities of purgatives, are those most likely to do this to themselves. They are characteristically evasive or downright misleading about their use of purgatives, so that the true cause of the potassium deficiency and renal failure may not be detected for a considerable time, even with the patient in hospital.

There are two other situations in which renal failure is caused by excessive *renal* loss of potassium, diabetic ketosis and primary aldosteronism. In diabetic ketosis (p. 318) the potassium deficiency is only an incidental cause of renal failure and no diagnostic confusion is likely.

Renal failure due to primary hyperaldosteronism may be extremely difficult to distinguish from renal disease causing secondary hyperaldosteronism, when the associated renal ischæmia causes a release of renin and stimulation of the adrenal glands by angiotensin. In both there may be polyuria and thirst, low plasma potassium, hypertension and a raised blood urea. In primary aldosteronism, the hypertension is not usually malignant, whereas it is more often malignant with renal ischæmia. In addition the plasma sodium is higher (137–160 mEq./l.) in primary aldosteronism than in secondary aldosteronism (125–141 mEq./l.) though there is some overlap. On the other hand, the plasma potassium is lower (1·4 to 3·2 mEq./l.) in primary aldosteronism than in secondary aldosteronism (3·1 to 4·2 mEq./l.). One method of distinguishing between these two is to measure the plasma renin before and after 3 days on a low sodium diet; the second blood being taken on the third day, after standing for four hours. In primary aldosteronism the control plasma renin is low and it remains low. In secondary aldosteronism the control renin should be higher but the most characteristic finding is that it rises further after a low sodium diet and standing. A renal biopsy can sometimes help. If the structural changes are characteristic only of potassium deficiency, i.e. there is vacuolation of the tubule cells, particularly of the distal tubules, the hypokalæmia and renal failure may be due to primary aldosteronism. If the lesions are more extensive and include those of interstitial nephritis renal biopsy is of relatively little help, for such changes can follow potassium deficiency or they may be due to a long-standing chronic renal disease which may be the cause of the potassium deficiency.

Treatment

When renal disease is the cause of the potassium deficiency the only effective treatment is potassium replacement followed by the daily oral administration of sufficient potassium to balance the excess urinary loss.

Potassium chloride is clearly what is needed in nearly all instances, particularly at the beginning of treatment when there is a potassium and chloride deficit to be corrected. Solutions of oral potassium chloride however, have an unpleasant taste and enteric coated tablets produce sharply delineated zones of circatricial narrowing of the small bowel which may cause complete or partial obstruction. Recently "slow release" tablets of "wax" impregnated with potassium chloride (Slow K) have had some success. Once the initial potassium and chloride deficiency has been corrected, other salts of potassium can be used to prevent a deficit of potassium recurring. A mixture of potassium acetate, citrate and bicarbonate, 1 g. of each in 8 ml. of water, four times a day supplies 116 mEq. of potassium in a relatively palatable form. Mist. Pot. Cit. (B.P.) contains 3 g. of potassium citrate, i.e. 28 mEq. of potassium per 15 ml. which is about half an ounce; this is also well tolerated.

To prevent the onset of potassium deficiency during the early diuretic phase of acute tubular necrosis, it is usually only necessary to give plenty of orange and tomato juice, figs, apricots, dates and meat extract, all of which contain high quantities of potassium (p. 384).

When potassium deficiency is due to excess alimentary loss all that is required is to replace the potassium and stop any further loss; if the latter is not possible (e.g. intestinal fistulæ, gastric suction) potassium should be given intravenously at the same rate as it is being lost.

Potassium is best given intravenously when there is a good urine flow, in order that an excess plasma potassium may more easily spill over in the urine. It is also wise to avoid intravenous administration for 24 hours after any particular stress such as an operation, for at these times the plasma potassium is apt to be raised whatever the concentration in the cells. It should also be bourne in mind that in normal circumstances, though the total body potassium is about 2,500 mEq., the amount in the extracellular fluid is only 75 mEq.

and that death occurs if it rises to 150 mEq Cardiac arrest from hyperkalæmia occurs at plasma levels of 9–10 mEq /l, it is generally *wise not to give potassium intravenously at a greater rate than* 25 mEq per hour It is also best to limit the concentration of the fluid to 40 mEq /l, for higher concentrations are liable to cause painful spasm of the vein

If a patient suffering from a pure potassium deficiency is given *saline instead of potassium there is likely to be increased sodium* retention with œdema and an increased urinary excretion of potassium The administration of sodium bicarbonate should also be avoided for this induces a severe alkalosis

CALCIUM

A raised urinary excretion of calcium may cause renal failure irrespective of the overall calcium balance The reason for this is not known but it is probably related to an intracellular accumulation *of calcium ions in the tubules This is in contrast to the renal failure* of potassium deficiency (see above) which is due to an intracellular deficiency of potassium ions or the renal failure of sodium deficiency which is due to contraction of the extracellular fluid volume and renal vasoconstriction

The following conditions are associated with a high urinary calcium excretion and renal failure

Increased Urinary Excretion of Calcium *due to* Renal Failure

The only renal disease known to cause a great increase in urinary calcium excretion is renal tubular acidosis (p 216)

Increased Urinary Excretion of Calcium as a cause of Renal Failure

(a) Following increased calcium absorption

1 *Compulsive milk drinking*
2 Vitamin D intoxication
3 Sarcoidosis
4 Idiopathic hypercalcæmia of infants

(*b*) Following an increased rate of bone decalcification

1 Hyperparathyroidism
2 Diffuse carcinomatosis of bone
3 Myelomatosis
4 Immobilisation
5 Paget s disease

The Effect of Hypercalcæmia on Renal Structure and Function

In the early stages renal biopsy may show no abnormality, but later precipitated calcium can be seen as clumps between and across the nephrons, and as a fine dusting of the tubule cells and their basement membranes. The early lesions are in the collecting ducts, distal tubules and ascending loops of Henle, later the whole nephron is involved. Some tubules eventually atrophy, and varying numbers of glomeruli become structureless round eosinstaining masses. In long-standing cases the deposition of calcium in the kidney can be seen radiologically.

Hypercalcæmia from any cause *except hyperparathyroidism* increases urinary hydrogen ion excretion. Ammonia excretion therfore rises and urine *p*H falls, while plasma bicarbonate and *p*H rise and there is an alkalosis. (This acceleration of hydrogen ion secretion by the tubule is paralleled by an increase in hydrogen ion secretion by the gastric mucosa so that hypercalcæmia is often associated with epigastric pain, dyspepsia and peptic ulcers.) The cause of this acceleration of hydrogen ion secretion is unknown, it may be due to stimulation of carbonic anhydrase activity. In early hypercalcæmia therefore (with the exception of hyperparathyroidism), there may be the paradoxical finding of a raised plasma bicarbonate with a low urine *p*H. On the other hand, parathormone inhibits hydrogen ion excretion so that when hypercalcæmia is due to hyperparathyroidism there is a rise in urine *p*H and a tendency for the plasma bicarbonate to fall.

Hypercalcæmia and hypercalcuria from any cause profoundly impair the kidney's ability to concentrate the urine; frequently the urine concentration remains fixed at a concentration well below that of plasma. The impaired ability to concentrate is related to the hypercalcuria as well as the hypercalcæmia and may therefore occur without hypercalcæmia. If hypercalcæmia persists there is a fall in glomerular filtration rate, a rise in blood urea and proteinuria. At first the blood urea is only moderately raised to 50–60 mg./100 ml., and there is then a marked discrepancy between the severe impairment in concentrating ability and the modest rise in blood urea. Gradually so many nephrons are destroyed that eventually the findings are the same as those in chronic renal failure from any cause. At this point the increasing impairment of hydrogen ion secretion and ammonia production of renal failure is superimposed upon the effect of hypercalcæmia and if the plasma bicarbonate was raised it now falls to normal or below.

Clinical Features Associated with Hypercalcæmia and Hypercalcuria

As the renal failure is only related to the high urinary excretion of calcium and not to negative calcium balance (unlike potassium and sodium), the general signs and symptoms vary widely from one cause to another For instance, if the hypercalcuria is secondary to bone disease there will be a negative calcium balance and signs and symptoms of bone softening or fractures, whereas if hypercalcuria is due to excessive intestinal absorption of calcium there will be calcium equilibrium and no signs or symptoms of bone disease

There is always thirst, polydipsia and polyuria These are often of such severity that the patient may at first be thought to be suffering from diabetes insipidus (p 306)

Hypercalcuria is usually present when the serum calcium is raised, it may also be present without such a rise Alternatively, if the glomerular filtration rate is sufficiently depressed there may be hypercalcæmia without hypercalcuria Occasionally when the urinary excretion of calcium is extremely high i e around 1 000 mg a day (on a normal diet the usual range is 80–400 mg) the urine upon standing will develop a thin white chalky precipitate which is characteristic.

Ætiology and Diagnosis

Increased Urinary Excretion of Calcium as a cause of Renal Failure

(a) *Following Increased Calcium Absorption* In compulsive milk drinking vitamin D intoxication sarcoidosis idiopathic hypercalcæmia of infants and there is an increased alimentary absorption of calcium and the following sequence hypercalcæmia → hypercalcuria → renal failure

Compulsive milk drinking is a rare condition which initially, can easily be overlooked for the patient may fail to disclose his idiosyncrasy or he minimises its extent Frequently the milk drinking begins because of recurrent dyspepsia but as the amount taken increases and hyper calcæmia develops the dyspepsia becomes worse The fact that these patients are also apt to take larger quantities of alkalis may increase the liability of calcium to be deposited in the kidney They are frequently admitted with advanced renal failure and alkalosis Diagnosis may be difficult for by this time glomerular filtration rate is so depressed that there is no hypercalcuria and in addition the patient is now so ill and nauseated that his compulsion for milk is less pressing Hypercalcæmia is usually present and often there are widespread deposits of calcium in the skin joints, corneæ and lungs

Unequivocal vitamin D intoxication is rare In adults it occurs as a form of food fad, and in infants and children from over solicitous motherly attention There is increasing evidence that infants and children may normally ingest larger quantities of vitamin D than are necessary, for not only is it given as concentrated cod and halibut liver oil, but much of the food they eat, such as milk preparations and cereals, may have vitamin D added in substantial quantities. This excess may be the precipitating cause of the increased calcium absorption of idiopathic hypercalcæmia of infants. Recently the vitamin D content of commercial milk preparations and cereals has been reduced.

The increased calcium absorption of sarcoidosis also appears to be due to vitamin D; not excess ingestion, but rather to a hypersensitivity to normal amounts either in the food or following exposure to sunlight. The increased absorption and hypercalcuria can be controlled by adrenal steroids, 150 mg. of cortisone per day for 10 days causes a fall in plasma calcium and in urinary calcium excretion.

(*b*) *Following Increased Rate of Bone Decalcification.* There are three principal conditions to be considered: hyperparathyroidism, diffuse carcinomatosis of bone and myelomatosis.

The diagnosis of hyperparathyroidism depends on the finding of a raised plasma calcium, a low plasma phosphate, and hypercalcuria; the characteristic periosteal erosions in the bones of the hands, bone cysts, a raised alkaline phosphatase and recurrent renal calculi may also occur. It is the condition which gives rise to the highest serum calcium concentrations; sometimes over 20 mg. per 100 ml. Acute hyperparathyroidism with severe prostration, muscular weakness, pains and tenderness, vomiting, cardiac failure, dyspepsia, polyuria and polydipsia may not be recognised, unless the diagnosis is suspected on every occasion that there is unexplained thirst and polyuria. Radiological bone lesions may be absent both in acute and chronic hyperparathyroidism, which makes the differentiation from sarcoidosis difficult. The confusion is greatest if renal failure is moderately advanced, for this occasionally causes the plasma phosphate to rise and thus obscure one of the most characteristic signs of hyperparathyroidism.

Diffuse carcinomatosis of bone is usualy identified by X-rays of the skeleton and there may be an erythroblastic anæmia.

Renal failure associated with myelomatosis is sometimes due to increased urinary calcium excretion. Hypercalcæmia may precipitate a rapid deterioration of renal function.

Treatment

The treatment of renal tubular acidosis is discussed in Section 17.

The increased calcium absorption in sarcoidosis is treated with cortisone; as this functional peculiarity is often phasic, treatment should be interrupted now and again to see if it is still necessary.

Idiopathic hypercalcæmia of infants will usually respond in a few weeks when treated with either a low calcium diet or cortisone; the latter allows a much greater flexibility in the diet, and calcium ingestion need only be controlled to a limited extent.

Hyperparathyroidism is treated by removal of adenomata or hyperplastic glands. Acute renal failure following operation may occur and is particularly dangerous, for the falling serum calcium and rising potassium summate in their ill effects. Patients suffering from compulsive milk drinking or vitamin D intoxication are usually only in need of advice.

MAGNESIUM

Increased Urinary Excretion of Magnesium due to Renal Failure

Very occasionally a severe exacerbation of acute upon chronic pyelonephritis in a patient with established chronic renal failure may cause a reversible urinary leak of magnesium. This is nearly always associated with a simultaneous equally reversible leak of sodium and potassium and a profound hypocalcæmia. The diagnosis is most easily made by measuring the plasma magnesium which will be low. Symptoms of magnesium deficiency develop at plasma levels of magnesium well below 1 mEq./l. These consist of gross tremors, confusion with panic attacks, vomiting, fasciculation, hyporeflexia and usually, but not always, a positive Trousseau and Chvostek's sign. It is interesting that in magnesium deficiency with hypocalcæmia the plasma calcium may rise upon giving magnesium chloride.

Chronic renal failure from other causes such as persistent glomerular nephritis has on rare occasions been described as causing a persistent urinary leak of magnesium.

Renal Failure due to Magnesium Deficiency

This has not been described in man. In animals magnesium deficiency causes an increased potassium excretion with potassium depletion, together with a hypercalcæmia and hypercalcuria. Renal failure develops eventually. In the earlier stages the potassium deficiency is associated with an unimpaired ability to concentrate. The reason for this is not known. There may be a human parallel. It is known that hyperaldosteronism causes an increased urinary excretion of magnesium, and it is also established that some patients with hyperaldosteronism may have a potassium deficit without an impairment in the ability to concentrate. It is possible that this may be due to the associated magnesium deficiency.

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17

SELECTIVE DEFECTS OF TUBULAR FUNCTION

SELECTIVE functional defects of the renal tubules may be either congenital or acquired.

CONGENITAL DEFECTS OF TUBULAR FUNCTION

The following is a modification of Jackson and Linder's classification of these conditions.

SINGLE DEFECTS	
Impaired ability to reabsorb	
Water	Renal diabetes insipidus
Phosphate	Vitamin D resistant rickets, familial hypophosphatæmia
Glucose	Renal glycosuria
Cystine and other amino-acids	*Simple congenital cystinuria*
Xanthine	Xanthinuria
Calcium	Idiopathic hypercalcuria
Excessive reabsorption of	
Phosphate	Pseudohypoparathyroidism
MULTIPLE DEFECTS	
Impaired ability to reabsorb	
Phosphate, glucose and amino-acids	*Idiopathic de Toni-Debré-Fanconi syndrome*
Impaired ability to achieve a high hydrogen ion and osmotic gradient	Renal tubular acidosis, Hyperchloræmic acidosis, Hyperchloræmia nephrocalcinosis

Impaired Ability to Reabsorb Water

This condition is known as renal or nephrogenic diabetes insipidus. It is described on p. 307.

Impaired Ability to Reabsorb Phosphate

This condition is also known as vitamin D resistant rickets or familial hypophosphatæmia. These names describe the two main clinical features of the disease and avoid any precipitate precision about its ætiology. In addition to the tubular abnormality there is also an impaired ability of the intestines to absorb calcium and occasionally phosphate. The cause of the tubule's impaired ability to reabsorb phosphate is not clear. It is possible that it is due to a secondary hyperparathyroidism compensating for a primary impairment in the ability to absorb calcium from the gut. In favour of this explanation is the fact that (1) in a few cases exploration of the neck has demonstrated parathyroid hyperplasia; (2) secondary hyperparathyroidism is known to occur in nutritional osteomalacia; and (3) if parathyroid function is inhibited by a twelve-hour intravenous infusion of calcium, tubular reabsorption of phosphate rises precipitously until very little phosphate appears in the urine (in one patient there was no phosphate in the urine for twelve hours). If this explanation is accepted familial hypophosphatæmia is a disease of the small bowel in which the kidneys are normal. It is then difficult to explain why, very occasionally, a patient may also have tubular glycosuria or aminoaciduria. Whatever the true explanation of this syndrome the remarkable ability to reabsorb phosphate which follows an intravenous infusion of calcium makes it most unlikely that there is a primary defect in the tubules capacity to reabsorb phosphate.

The disease is nearly always inherited as a sex-linked dominant characteristic, i.e. it appears to be placed on the X chromosome. This conclusion follows from the fact that all the daughters of the male sufferers tend to be affected but none of the sons, whereas half the sons and half the daughters of the female sufferers are affected.

The classical syndrome is that of dwarfism in a young boy with late rickets (around the age of four to eight years), but many affected individuals, particularly women, are healthy and have no skeletal changes. Regardless of bone changes the presence of the disease in the affected person is recognised by the low concentration of serum phosphorus and the diminished ability of the tubules to reabsorb phosphate. The tubular abnormality is detected by one or more of the several methods described earlier (p. 76). For instance, when the condition is particularly severe urinary phosphate excretion continues when the concentration of serum phosphorus is below the normal phosphate threshold of 2·1 mg./100 ml. Urinary calcium excretion is always low. The glomerular filtration rate is unimpaired and the concentration of serum calcium is usually normal though occasionally it is raised in the affected children (i.e. under the age of 15 years) and usually normal thereafter, and a bone biopsy shows the appearance of osteomalacia. Plasma alkaline phosphatase is raised. The impaired intestinal absorption of calcium has been demonstrated in patients with skeletal changes. There are, as yet, no reports of calcium balance studies in affected individuals with normal bones.

Treatment. The aim of treatment is to increase calcium absorption and thus increase the deposition of calcium in the bones. This is attempted either by giving calcium alone or in combination with calciferol; sometimes calciferol is given with phosphate; and occasionally phosphate alone is given. The short-term efficacy of treatment can be gauged by following the plasma alkaline phosphatase and the urinary excretion of calcium. The former should fall and the latter should rise. At longer intervals serial X-rays of bone will demonstrate whether the aim of treatment is being achieved.

Calcium lactate 15–20 g /day may be sufficient. Vitamin D is given in large amounts such as calciferol 2–5 mg. per day. Sometimes the calciferol is of most benefit if given with a high intake of dietary phosphate and the administration of $Na_2HPO_4\ 2H_2O$ 10 g per day Calciferol may be difficult to control for it appears that the patient's sensitivity may fluctuate so that he may either develop hypercalcæmia which indicates that too much is being given or a rise in the plasma alkaline phosphatase which means that the dose of calciferol is insufficient. Occasionally the administration of large amounts of phosphate alone without vitamin D has caused a radiological improvement in the bone lesions This only occurs if the urinary calcium excretion is high or " high normal ". As treatment progresses there is usually no significant change in plasma phosphorus or calcium though the tubule's ability to reabsorb phosphate often improves Frequently the condition does not respond or there is only a transient improvement

Impaired Ability to Reabsorb Glucose

This condition is known as renal glycosuria and is described on p. 316

Impaired Ability to Reabsorb Cystine and Certain Other Amino-acids

There are two principal conditions in which cystine appears in the urine. In one, which is usually known as cystinuria, the metabolism of cystine is normal, but an isolated abnormality of tubular function allows large amounts of cystine, and the dibasic amino acids arginine, lysine and ornithine to be excreted in the urine Patients suffering from cystinuria also have a defect of intestinal absorption for cystine, arginine, lysine and ornithine. The other condition in which cystine may appear in the urine is best called cystine storage disease, but is also known as one cause of Fanconi's syndrome. The important disturbance is a defect in protein and amino-acid metabolism which causes a widespread deposition of cystine throughout the body. At the same time there is deposited in the tubules an unidentified metabolite which causes the abnormalities of the tubular function. These include cystinuria and other amino-acidurias, phosphaturia, glucosuria and sometimes an impaired ability to acidify and concentrate the urine

Cystinuria. In this condition cystine appears in the urine together with arginine, lysine, and ornithine. The excretion of cystine averages 0·5 to 1 g. per day. A solution of cystine at a *p*H 5 to 7 becomes saturated around 300 to 400 mg./l. and tends to come out of solution when it is acid. In patients with cystinuria it is extremely likely, therefore, that at night when the urine is both concentrated and acid it becomes supersaturated, which explains why the clinical complication of the disease is the recurrent formation of renal calculi made of cystine which are radio opaque. The other amino-acids which appear in the urine are freely soluble and do not form calculi, nor does their excess loss seem to cause any detectable clinical abnormality. The first cystine stone commonly presents during childhood or infancy; it is rare for it to do so after the age of 30. It is a surprising feature of cystinuria that though renal calculi may recur over a number of years, renal infection is unusual.

Treatment consists in drinking 3 l. of fluid throughout the 24 hours, including two glasses of water upon going to bed and another two after midnight, when the first two have usually forced the patient out of bed to empty his bladder. It is claimed that such treatment will not only prevent the formation of new stones but it will also "dissolve" those present. If, on the other hand, this is insufficient to prevent precipitation of cystine the urine is made alkaline by the administration of 15 g. per day of sodium bicarbonate.

Cystinuria can also be treated by the oral administration of D-penicillamine at regular intervals throughout the day. The relatively insoluble cystine is then converted to the highly soluble penicillamine-cysteine-disulphide. The dose of D-penicillamine has to be adjusted to the rate of cystine excretion. This treatment is much more convenient for the patient but at the moment (i.e. 1966) the cost of the D-penicillamine is approximately £500 per patient per year.

Cystine Storage Disease and Fanconi's Syndrome. This condition is discussed on p. 214.

Impaired Ability to Reabsorb Xanthine

This condition is usually known as xanthinuria. It is due to two functional defects. First, an absence of xanthine oxidase in the liver so that the conversion of xanthine to uric acid is blocked; and, secondly, a tubular defect of xanthine reabsorption. The clearance of xanthine equals that of the glomerular filtration rate. Large quantities of xanthine therefore appear in the urine but only traces of uric acid, and the blood uric acid is exceedingly low. Occasionally, xanthine renal calculi, translucent to X-rays, may be formed. As xanthine is much more soluble in alkaline urine, treatment consists in the administration of sodium citrate or bicarbonate to those patients who are apt to form stones

Impaired Ability to Reabsorb Calcium

This condition is known as idiopathic hypercalcuria It is characterised by a calcium excretion greater than 400 mg per day The alimentary absorption of calcium however is also raised so that the patient is in calcium balance and there are no bone changes Plasma calcium is normal but in about 10–20 per cent of patients the plasma *phosphate is low (i e below 2 6 mg /100 ml) A minority of patients* with idiopathic hypercalcuria develop renal stones

There is still considerable controversy about the cause of this disturbance It has not yet been possible to determine whether the primary defect is a decreased tubular ability to reabsorb calcium or an increased intestinal absorption of calcium Or whether the increased intestinal absorption of calcium is secondary to hyperparathyroidism The position is not made clearer by the finding at operation that in a small proportion of those patients who have a low serum phosphate the parathyroids are hyperplastic and that such patients are improved by partial parathyroidectomy

Treatment. *Unless the patient suffers from renal stones treatment is* not required If stones are being formed and the patient has a low plasma phosphate *the neck should be explored for parathyroid hyperplasia* Otherwise the aim of treatment has been to try and lower urinary calcium excretion in an attempt to prevent the formation of new stones or to produce regression of existing stones The various ways this has been attempted include (1) a low calcium diet (2) the use of oral sodium phytate (6–8 g per day with meals) or cellulose phosphate (12–15 g per day with meals) to bind calcium in the lumen of the intestine and so reduce calcium absorption (3) the use of bendrofluazide (5–7 mg per day) which reduces calcium excretion by some unknown mechanism, (4) a low phosphate diet together with the administration of aluminium hydroxide gel (100 ml /day of Aludrox) to bind phosphate in the intestinal lumen (this reduces phosphate absorption and also depresses calcium absorption), (5) the admini*stration of oral sodium bicarbonate (5–10 g per day) to alkalinise the* urine for this also reduces urinary calcium excretion Some of these *manoeuvres are tedious or unpleasant and some occasionally cause* uncomfortable side effects They are sometimes capable of lowering urinary calcium excretion to *very low levels e g below 50 mg per day* Nevertheless there is no convincing evidence that this influences the rate of stone formation or causes any regression or disappearance of existing calcified stones A few patients in whom urinary calcium excretion has been persistently reduced to below 40 mg. per day have still developed new stones, though these were uncalcified.

Some authorities advise the drinking of large volumes of water to prevent the urine becoming concentrated and thus to minimise the chances of calcium precipitating. This is probably good advice but it is important to remember that some water supplies contain large amounts of calcium (e.g. London, 10 mg./100 ml.) and that the ingestion of large amounts of such water may substantially increase urinary calcium excretion.

Excessive Reabsorption of Phosphate

This extremely rare condition is also known as pseudohypoparathyroidism. The patient presents with attacks of tetany or fits, and the diagnosis is made by finding a high plasma phosphate concentration and a low serum concentration of calcium which are not influenced by injections of parathormone. There are no other abnormalities of renal function. These patients have characteristic round flat faces with small bulbous noses, thin straight mouths, and strabismus; they also have short stumpy hands with stunted metacarpals. They are usually mentally retarded.

Impaired Ability to Reabsorb Glucose, Amino-acids and Phosphate

This combination of functional defects is often defined as Fanconi's syndrome. In nearly every instance it is due to the toxic effects upon the tubule of either a metabolite or an exogenous poison (p. 219). There are a few isolated cases in which up till now it has not been possible to find such a cause. Such patients are sometimes referred to as suffering from an Idiopathic de Toni-Debré-Fanconi syndrome; there is little evidence that this syndrome is inherited.

The best known example of Fanconi's syndrome is the one associated with the widespread deposition of cystine (cystinosis). This is an inborn error of metabolism which is inherited as a simple Mendelian recessive. The tubular defects do not appear until the end of the first six months of life. The amino-aciduria includes a wide variety of amino-acids, but the amount excreted is much less than in cystinuria (p. 212). In addition there are often other tubular defects including an impaired ability to acidify and concentrate the urine and a renal leak of potassium. These defects may follow from the initial tubular damage and they may in their turn cause further tubular lesions. This vicious spiral can sometimes be arrested and many of the tubular defects reversed by therapeutically correcting their consequences, i.e. if the phosphate loss is corrected with vitamin D and the acidosis with alkalis, the amino aciduria may be lessened or abolished and a potassium leak may be arrested, potassium replacement has sometimes cured the impaired *ability to acidify and concentrate* Apart from these characteristic tubular abnormalities there is always proteinuria, characteristically there is high excretion of a_2 globulin Glomerular filtration rate is always impaired

It has been shown by means of microdissection of individual nephrons from patients who have died from cystinosis that the condition is associated with a characteristic structural lesion (Fig 17 1) The proximal tubule is shorter than normal and is connected by an abnormally long and narrow neck quite unlike anything seen in normal subjects The relevance of this finding is equivocal for a similar finding has been found in cases of congenital nephrotic syndrome and other diseases which have none of the tubular defects associated with the Fanconi syndrome

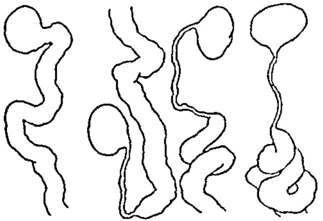

Fig 17 1 Fanconi's syndrome Outline drawing of the first part of three microdissected nephrons showing that the glomeruli are attached by a *narrow elongated neck to the proximal convoluted tubule A normal* nephron is seen on the left (Clay Darmady and Hawkins 1953 *J Path Bact*)

Cystinosis first makes itself manifest either in infancy or occasionally in childhood *The clinical picture is one of thirst, polyuria failure to* thrive and rickets The children are characteristically short and squat the blood urea is always raised the plasma potassium often below 3 mEq/l and occasionally there is a hyperchloraemic acidosis Urinary calcium excretion is low and the alimentary absorption of calcium is impaired Diagnosis depends upon finding opaque deposits of cystine in the cornea or the finding of cystine in a liver or lymph node biopsy Infants may die of dehydration with electrolyte imbalance Those who survive into childhood die of progressive chronic renal failure before puberty.

Treatment of the defect of phosphate reabsorption with vitamin D, calcium and sodium phosphate; of the renal tubular acidosis with alkalis, and of the potassium defect have been mentioned earlier. The administration of potassium should be increased gradually for hyperkalæmia is easily induced.

Impaired Ability to Achieve a High Hydrogen Ion and Osmotic Gradient

This condition is also known as renal tubular acidosis, hyperchloræmic acidosis and hyperchloræmic nephrocalcinosis. It is also known as renal acidosis, an unfortunate term which invites confusion with the acidosis found in chronic renal failure (p. 167). The best label is that of renal tubular acidosis.

The outstanding abnormalities of tubular function are an impaired ability to acidify and concentrate the urine. The inability to lower the urine *p*H is not due simply to an impaired ability to transfer hydrogen ions from the cell to the tubular fluid for if an artificially high urinary excretion of phosphate is induced by giving large amounts of phosphates, the rate of urinary hydrogen ion excretion can be raised to normal levels. In these circumstances, of course, the titratable acidity rises without an appreciable change in urinary *p*H, for the hydrogen ions are buffered by the phosphate as they emerge into the tubular fluid. It seems therefore that the functional impairment in renal tubular acidosis is an inability to produce and maintain a hydrogen ion gradient between the tubule lumen and the cell. With normal quantities of buffer in the urine the impaired ability to lower the urine *p*H results in a reduced excretion of titratable acid. Ammonia excretion is usually normal in relation to the urine *p*H, but as the urine *p*H cannot be reduced the absolute excretion of ammonia is nearly always low (Fig. 17.2). The combination of a reduced titratable acid and ammonia excretion causes a serious diminution in total hydrogen ion excretion and a retention of hydrogen ions. In addition to the impaired ability to produce and maintain a high hydrogen ion gradient across the tubule wall the tubules are also unable to produce a high osmotic gradient so that there is an impaired ability to produce a highly concentrated urine.

Renal glycosuria and amino-aciduria do not occur and the maximal capacity to excrete PAH and reabsorb phosphate is normal, but other abnormalities of tubular function may be present. There can be an increased urinary calcium excretion, and nephrocalcinosis; often both are present together, but they can occur independently. Their cause is unknown It has been suggested that the nephrocalcinosis is due to the reduced excretion of citrate which accompanies the persistently raised urinary *p*H The increased calcium excretion is often associated with osteomalacia There may also be an increased excretion of potassium giving rise to potassium deficiency Again the cause is unknown, possibly it is related to the intracellular acidosis

The fall in plasma bicarbonate which accompanies the retention of hydrogen ions is accompanied by a compensatory increase in plasma

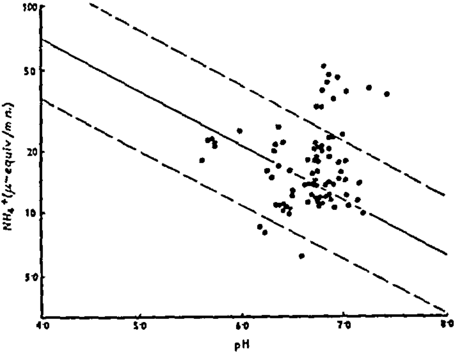

FIG 17 2 Renal tubular acidosis Relation between the excretion of ammonium and urine *p*H The calculated regression line and 95 per cent range in normal individuals are shown Each point represents an observation made in a patient suffering from renal tubular acidosis after the oral ingestion of a single dose of ammonium chloride (Wrong and Davies 1959 *Quart J Med*)

chloride concentration Often therefore the diagnosis is first suspected by a finding of hyperchloræmic acidosis Usually the creatinine clearance and blood urea are either normal or only moderately impaired so that the fall in plasma bicarbonate is out of proportion to the mild rise in blood urea e g a plasma bicarbonate of 10 mEq /l with a blood urea of 40 mg per 100 ml The diagnosis is confirmed by finding that though there is a systemic acidosis the urine *p*H is around 6 5 and that the urinary excretion of ammonium and hydrogen ions is low Upon giving a single dose of ammonium chloride by mouth (p. 65) there is usually little change in the urine *p*H and the excretion of ammonia rarely rises above 50 μEq./min.; in children the urine *p*H is usually greater than 7·4 and there is therefore extremely little excretion of ammonium. The impairment in the ability to concentrate the urine following dehydration or after the administration of vasopressin is equally striking, in contrast to the almost normal glomerular filtration rate, e.g. creatinine clearance 90 ml./min., urine osmolality after vasopressin 420 m.osmole/kg. (S.G. 1·013).

Children (usually male infants) are affected mainly by the inability to concentrate the urine and the retention of hydrogen ions, so that they usually present with failure to gain weight and dehydration accompanied by vomiting and constipation; nephrocalcinosis, calcium deficiency and potassium deficiency are uncommon. It is interesting that in Europe the incidence of so-called primary infantile renal tubular acidosis suddenly declined after 1954. This decline and the transient nature of the disturbance in infants, suggests that in many instances it is due to an environmental factor. Nevertheless, none has been discovered except for the occasional case due to mercurial poisoning with dusting or teething powders.

In adults, the most frequent clinical presentation is that of osteomalacia, or hæmaturia and renal infection due to nephrocalcinosis, and renal calculi developing in a woman. In a few adults the disease has only been discovered accidentally because an abdominal X-ray, taken for some unrelated purpose, has shown the appearance of nephrocalcinosis. In some of these patients the tubule's impaired ability to acidify and concentrate the urine has not been accompanied by hydrogen ion retention so that the plasma *p*H and bicarbonate have been within normal limits. It has been found that this paradoxical situation is due to an increased tubular capacity to excrete ammonia. It is not known whether these findings represent a stage in the chronological progress of the condition or a separate disorder.

Treatment consists in the administration of alkalis (sodium bicarbonate or citrate) for the acidosis; citrate and citric acid are given to increase the urinary excretion of citrate so as to prevent the further precipitation of calcium in the renal parenchyma, e.g. sodium citrate 98 g., citric acid 140 g., water to 1 litre, 50–100 ml. per day. The administration of alkalis also decreases the rate of urinary excretion of calcium. In addition, calcium deficiency is treated with calcium lactate and calciferol, and potassium deficiency with potassium citrate. At first it may be necessary to give as much as 200 mEq. of potassium per day; during this time the administration of sodium bicarbonate and citrate is decreased. Later a patient may need 150 mEq. of sodium and 50 mEq of potassium as bicarbonate or citrate Renal infections should be treated with continuous antibiotics but sulphonamides should be avoided for their inhibiting effect on carbonic anhydrase aggravates the impaired ability to excrete hydrogen ions *Renal tubular acidosis in children can usually be controlled and often* there may be a spontaneous recovery In adults treatment may be more difficult and recovery is unusual

ACQUIRED FUNCTIONAL DEFECTS OF THE RENAL TUBULE

Single and multiple disorders of tubular function may be caused by a wide variety of conditions The following list which is not exhaustive shows that most of the disorders are the same as those that are genetically determined

SINGLE DEFECTS		
Impaired ability to reabsorb		Due to
Water	e g	(*a*) excess intake of water (compulsive water drinking) (*b*) sickle cell anaemia.
Sodium	e g	(*a*) chronic pyelonephritis. (*b*) cystic disease of the renal medulla
Potassium	e g	very rarely in cases of persistent glomerular nephritis or pyelonephritis
Phosphate	e g	(*a*) potassium deficiency (*b*) acidosis.
Amino-acids	e g	galactosaemia
Impaired ability to secrete ammonia (p. 359)		
MULTIPLE DEFECTS		
Impaired ability to reabsorb		
Amino-acids glucose phosphate and water	e g	(*a*) cystinosis (*b*) heavy metal poisoning lead cadmium *mercury* copper (Wilson s disease) (*c*) glycogen storage diseases (*d*) multiple myelomatosis
Impaired ability to achieve a hydrogen ion and osmolar gradient	e g	(*a*) potassium deficiency (*b*) chronic pyelonephritis (*c*) interstitial nephritis (*d*) mercury

It is not proposed to discuss these conditions except to stress that it is often difficult to distinguish whether a tubular defect is congenital or acquired; that often acquired lesions are superimposed upon congenital ones; and that treating the metabolic disorder caused by a tubular defect may not only cure the disorder but may also improve or abolish the original tubular abnormality which was its cause.

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18

RENAL FUNCTION AND METABOLIC ALKALOSIS

THE normal kidney's ability to deal successfully with a severe, persistent metabolic alkalosis is now well recognised. For instance, it has been shown that if patients suffering from peptic ulceration are treated with a continuous intragastric drip of 1,000 mEq. of sodium bicarbonate (84 g.) per day for three weeks there is a persistent rise in plasma bicarbonate, but no apparent change in renal functional efficiency, and in fact the glomerular filtration rate tends to rise and the blood urea to fall.

Nevertheless, in clinical practice the combination of alkalosis and renal failure occurs relatively frequently, and until recently it has been considered that the alkalosis was the cause of renal failure. The evidence mentioned above, however, contradicts this conclusion and the true position is more complex. Excluding increased ingestion of sodium bicarbonate, metabolic alkalosis is caused by either a deficiency of chloride, hydrogen or potassium ions, or very occasionally by a rise in plasma calcium concentration (p. 58). The connection between potassium deficiency and renal failure has been discussed previously (p. 200) while the connection between chloride and hydrogen ion deficiency and renal failure is best discussed in relation to the most common syndrome in which renal failure and alkalosis occur, i.e. pyloric obstruction, in which it will be seen that potassium deficiency may also contribute to the alkalosis, and the renal failure.

Pyloric Obstruction

Gastric juice contains water in which there are approximately 145 mEq./l. of chloride, 83 mEq./l. hydrogen ions, 50 mEq./l. of sodium, and 12 mEq./l. of potassium. Following the persistent vomiting of pyloric obstruction there develop deficiencies of water, hydrogen ions, chloride, sodium and potassium and, occasionally, there is the further complication of a gastro-intestinal hæmorrhage. Each of these gives rise to its own sequence of disturbance in body fluids, and renal function. It is important to realise that the direction of some of the renal functional disturbances depend on the pattern of the deficiencies, i.e. there may be oliguria or polyuria, an alkaline urine or an acid urine.

The relative proportions of these deficiencies determine which functional changes will predominate.

Fig. 18.1 illustrates the changes which may occur.

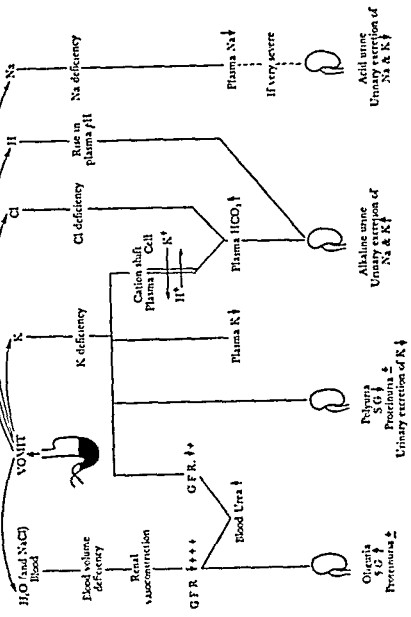

FIG. 18.1 Changes in plasma concentrations, and renal function which may occur as a consequence of the persistent vomiting of pyloric obstruction

Factors Involved in the Renal Failure of Pyloric Obstruction

Water and Blood Loss. The continuous loss of water (with sodium and chloride) reduces the volume of all fluid spaces including the blood volume, and this is followed by consequences which have been described previously, i.e. renal vasoconstriction → reduced glomerular filtration rate → rise in blood urea. These changes will be more pronounced if there is also gastro-intestinal bleeding; in rare instances acute renal failure develops. Usually the renal ischæmia stops short of tubular necrosis and there is only *oliguria* with a urine concentration which tends to be raised.

Hydrogen Ion Loss. The loss of hydrogen ions raises the plasma *p*H, slows respiration and raises pCO_2. The rise in pCO_2 then causes the proximal tubule to increase its secretion of hydrogen ions from the tubule cell into the tubule lumen so that there is an increase in the reabsorption of bicarbonate from the tubule lumen back into the plasma, and also an increase in generation of fresh bicarbonate by the tubule cells which is then secreted into the plasma. The loss of hydrogen ions in the gastric juice is therefore one cause for the rise in plasma bicarbonate.

Chloride Loss. The loss of chloride ions lowers the plasma concentration of chloride and thus the chloride filtered at the glomerulus. If the concentration of plasma sodium has fallen to a relatively less extent, which is probable because of the greater quantity of chloride than sodium in gastric juice, then the proportion of sodium to chloride in the tubule fluid will have risen, i.e. there will be relatively less chloride to reabsorb than sodium. This will stimulate hydrogen ion secretion from the proximal tubule cell into the lumen and so increase bicarbonate reabsorption and generation (p. 58). This is another cause for the rise in plasma bicarbonate.

In addition, the lowered content of chloride in the tubular fluid in the proximal tubule, automatically reduces the amount of sodium that can be absorbed, for sodium reabsorption must stop as chloride and bicarbonate reabsorption become almost complete.

It follows that though the patient is sodium deficient (because of the loss of sodium in the vomit) proximal tubular reabsorption of sodium cannot be complete as it usually is in other forms of sodium deficiency (p. 58). Sodium therefore continues to be spilled over into the distal tubule. In the distal tubule however, sodium reabsorption is linked with an exchange for either potassium or hydrogen ions, and the relative quantities of potassium or hydrogen ions which are so exchanged depend on their intracellular concentrations. But in pyloric stenosis the patient is vomiting both hydrogen and potassium ions and he and his distal tubular cells will be deficient in hydrogen and potassium ions The sodium that spills over from the proximal tubule into the distal tubule therefore is either not reabsorbed or will be reabsorbed in exchange for potassium or hydrogen ions There is then the paradox that a patient suffering from sodium potassium and hydrogen ion deficiency may be excreting sodium potassium and an acid urine (see below) *The loss of sodium ions contributes to the reduction in intra cellular volume and therefore to the precipitation and perpetuation of renal failure The loss of potassium also contributes to the renal failure*

Potassium Loss The consequences of potassium loss on renal function have been described on p 200 There is some reduction in glomerular filtration rate but the most marked feature is *polyuria* with a urine concentration which remains iso- or hypotonic Plasma potassium is low and to compensate for this there is a shift of potassium from the intracellular space to the plasma and extracellular space and a reverse shift of hydrogen and sodium ions from the extracellular space *into the cells The loss of hydrogen ions from the plasma results in a* rise in plasma bicarbonate one other cause of alkalosis in pyloric obstruction

Sodium Loss There is an overall sodium deficiency mainly due to the vomiting of sodium in the gastric juice but compared with the extracellular fluid vomit contains relatively more water than sodium so that the concentration of plasma sodium sometimes rises Usually however the patient s thirst forces him to drink water and this selective partial replacement of water to the exclusion of sodium *lowers the plasma concentration of sodium below normal*

If sodium and potassium deficiency become sufficiently severe the *urine is acid* though the plasma is becoming increasingly alkaline This is due to the lack of available potassium on the cation exchange mechanism in the distal tubule If sodium reabsorption is nearly complete and there is no available potassium some of the sodium ions reabsorbed in the distal tubule will be replaced by hydrogen ions and the urine will become acid This phenomenon must also be related to the raised concentration of hydrogen ions within the tubule cells

Chronic Renal Disease *It is obvious that if there is some ante*cedent impairment of renal function the onset of pyloric obstruction and vomiting will cause a rapid deterioration of renal function

Alkalis and Milk. The most frequent accompaniment of pyloric obstruction is peptic ulceration for which patients take both alkalis and milk Once the glomerular filtration rate begins to fall because of dehydration or potassium deficiency the continued administration *of sodium bicarbonate is not only useless but rapidly aggravates the* alkalosis. The high intake of calcium which accompanies the large ingestion of milk and certain alkalies, such as calcium carbonate, may cause hypercalcæmia or at least hypercalcuria which is an additional cause for the renal failure and also for the rise in plasma bicarbonate.

Treatment of Metabolic and Renal Consequences of Pyloric Obstruction

Upon admission to hospital, most patients with benign pyloric obstruction cease to vomit and quickly begin to correct their electrolyte and water deficiencies almost unaided. During the first few days it is customary to wash out the stomach before meals. Water and food then pass through the pylorus and are absorbed in normal amounts; in such patients it is only necessary to make sure that they are given a mixed diet and that it is relatively low in protein until the glomerular filtration returns to normal levels.

Occasionally, however, it may be necessary to accelerate recovery by giving electrolytes and water intravenously or in additional amounts by mouth. Isotonic saline is given intravenously in sufficient quantities to correct hæmoconcentration, peripheral vein constriction and tachycardia. The administration of isotonic saline not only corrects the depletion of the extracellular fluid volume but also provides at least 30 mEq. of chloride per litre to correct the chloride deficiency. (One litre of isotonic saline contains 150 mEq. of sodium and 150 mEq. of chloride while plasma contains 140 mEq./l. of sodium and 100 mEq./l. of chloride.) Once the volume of the extracellular fluid is replenished the continued administration of saline rapidly cures any remaining chloride deficiency and metabolic alkalosis, for the sodium ion is excreted while the chloride is retained. It is always important to give potassium by mouth even if plasma potassium concentration is normal, for there may be potassium deficiency without much change in plasma potassium. If plasma potassium concentration is unequivocally decreased potassium chloride should be given intravenously in combination with isotonic saline or 5 per cent glucose. When there is severe potassium deficiency, sodium chloride should not be given without giving potassium simultaneously, for the administration of sodium chloride may increase the urinary excretion of potassium.

It is unnecessary and perhaps harmful to use ammonium chloride for the correction of a metabolic alkalosis due to vomiting. Surgery should be avoided until renal function has recovered and there is no longer any evidence of electrolyte deficiency.

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19

RENAL DISTURBANCES FOLLOWING IMPLANTATION OF THE URETERS INTO THE BOWEL

WHEN the bladder is severely diseased it may be necessary to transplant the ureters. They can be placed so that they open either on the skin surface, into the large bowel or into an isolated segment of the small bowel.

Ureterosigmoidostomy

This operation is almost inevitably followed by reflux of fæcal material up the ureters, and in addition some of the contents of the urine are reabsorbed on their way down the colon. The reflux causes severe renal infections while the reabsorption of urea, hydrogen ions and chloride also cause certain complications. The reabsorption of urea is responsible for a rise in blood urea regardless of any change in renal function. It is distinguished from a rise in blood urea due to a true depression in glomerular filtration by estimating the plasma creatinine, for creatinine is not absorbed from the bowel. The reabsorption of chloride ions is important because in the bowel they are reabsorbed to a greater extent than sodium; this mechanism and the reabsorption of hydrogen ions tend to cause hyperchloræmic acidosis. The acidosis is greatly aggravated by the simultaneous absorption of ammonium salts (p. 65) formed from the urine by urea-splitting bacteria in the urine. The steady infusion of urine into the colon can therefore be looked upon as equivalent to a continuous infusion of ammonium chloride. In addition to the acidosis the other important complications of ureterocolic anastomosis is potassium deficiency from excess loss of potassium in the fæces. It is not clear whether this is due to the inevitable pyelonephritis which accompanies this operation so that increased quantities of urinary potassium are delivered into the lumen of the bowel, or whether it is caused by the loss of large quantities of colonic mucus in the fæces due presumably to irritation of the bowel by urine.

If the patient is not to become acidotic and œdematous (from the sodium reabsorption) the kidneys have to compensate for the intestinal reabsorption by excreting increased quantities of urea, sodium chloride, hydrogen ions and ammonium After a few months the initial difference between the rates of chloride and sodium reabsorption becomes less marked and the tendency to acidosis ceases This compensation is accompanied by marked hypertrophy of the kidneys

The renal infection may be accompanied by partial or complete ureteric obstruction (occasionally both of these may have been present before operation due to the disease in the bladder) Both infection and ureteric obstruction impair tubular function including the ability to excrete hydrogen and ammonium so that they may cause a rapid onset of severe acidosis Infection may also cause a urinary leak of potassium The nausea of acidosis diminishes the spontaneous intake of water and potassium and eventually it may cause vomiting considerable dehydration and contraction of the extracellular fluid volume Dehydration renal infection ureteric obstruction and acidosis can each depress glomerular filtration rate together they may rapidly cause death from acute renal failure Alternatively the patient may present with hypokalæmic paralysis the symptoms of potassium deficiency being always more severe if there is an associated acidosis as opposed to the usual accompaniment to potassium deficiency which is an extracellular alkalosis

These hazards are encountered most frequently immediately or very soon after operation Occasionally a patient may remain well for several months and then suddenly become ill and develop an acidotic coma in a few days It is probable that these relapses are due to an exacerbation of renal infection course of antibiotics should be given even if there is no overt evidence of renal infection.

When the symptoms are more severe and include vomiting, dehydration and clouding of consciousness, the rapid administration of 1/6 molar sodium bicarbonate intravenously, alternating with 5 per cent glucose, if necessary, will usually cause a quick return of consciousness. If the renal damage is reversible the blood urea will also quickly return to normal. Antibiotics are again administered together with large quantities of sodium bicarbonate by mouth until the plasma bicarbonate is normal.

Ureteroileostomy

If the ureters are placed in an isolated segment of the ileum most of the complications listed above can be avoided. The hazards are similar to those in ureterosigmoidostomy and for the same reasons, but they occur less frequently and are less severe. This is because the urine is only in contact with the small segment of the ileum for a shorter time. And the intraluminal pressures in this segment are much lower than in the colon so that reflux is less of a problem.

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20

IMMUNOLOGICAL DISEASES OF THE KIDNEY

THE theory that the diseases included under this heading are due to abnormal antigen antibody responses is supported by much evidence and forms a good working hypothesis it has the merit of linking together a number of conditions which have many clinical and some histological features in common

The following conditions are discussed

(1) Glomerular nephritis
(2) Renal disturbances in polyarteritis nodosa
(3) Renal disturbances in diffuse lupus erythematosus
(4) Renal disturbances in subacute bacterial endocarditis
(5) Renal disturbances in anaphylactoid purpura
(6) Lung purpura with nephritis (Goodpasture s syndrome)

GLOMERULAR NEPHRITIS

This disease is subdivided into an acute and a persistent form Each has several clinical components

Glomerular Nephritis	*Presenting Renal Symptom*
Acute	Acute nephritic syndrome Acute renal failure
Persistent	Rapidly progressive renal failure Persistent proteinuria Recurrent hæmaturia Nephrotic syndrome *Chronic renal failure*

Persistent glomerular nephritis may follow acute glomerular nephritis Conversely, an attack of acute glomerular nephritis may be superimposed upon persistent glomerular nephritis

A wide variety of histological changes accompany these various clinical presentations The most characteristic occur in the glomeruli They include minor changes that can only be detected with the electron microscope The light microscopy changes are proliferation or swelling of the cells of the glomerular tuft reduplication or thickening of the basement membrane, infiltration with polymorphonuclear leucocytes capsular crescents, and fibrous tissue replacement. Eventually, as increasing numbers of nephrons are destroyed the general architecture of the kidney is barely recognisable. Usually the changes seen in acute glomerular nephritis and in the rapidly progressive form of persistent glomerular nephritis are sufficiently distinct to enable a fairly accurate correlation to be made between the histological appearances and the clinical features. The pattern of histological changes which accompanies the other clinical forms of persistent glomerular nephritis, however, gives little or no indication of the accompanying clinical features. The correlation between the histological changes and the clinical features are listed below:

HISTOLOGICAL CHANGES IN GLOMERULAR NEPHRITIS	ACCOMPANYING CLINICAL "RENAL" SYNDROME
1. Endothelial proliferation, reduplication and widening of basement membrane, polymorphonuclear infiltration and occasional capsular crescents.	Acute nephritic syndrome. Acute renal failure.
2. Same as 1, but more severe and associated with numerous large succulent crescents.	Rapidly progressive renal failure.
3. (*a*) No change with light microscopy. (*b*) Proliferation of endothelial cells. (*c*) Swelling and vacuolation of epithelial cells. (*d*) An even thickening of the walls of the glomerular capillaries. (*e*) Mixture of (*b*), (*c*) and (*d*). (*f*) Widespread destruction of renal architecture with fibrous tissue replacement.	Persistent proteinuria. Recurrent hæmaturia. Nephrotic syndrome. Chronic renal failure.

In the absence of a clear-cut denominator it is not obvious why these various renal disorders should be merged within one collective term. The reasons are histological, clinical and traditional.

Clinical. Patients suffering from acute glomerular nephritis may develop a nephrotic syndrome, while others with a nephrotic syndrome or with chronic renal failure due to glomerular nephritis may develop an acute nephritic syndrome. Such cases clearly defy rigid classification and can only be placed under one comprehensive term.

Traditional. It is traditional to group together all those elements which now comprise glomerular nephritis since it was in this manner that they were originally described by Bright. His account is given below. It is a descriptive compression of acute glomerular nephritis, and both the nephrotic syndrome and chronic renal failure of persistent glomerular nephritis as if they all three formed one continuous process.

in alternate ratio, sometimes without apparent relation. Again the patient is restored to tolerable health; again he enters on his active duties; or he is, perhaps, less fortunate; the swelling increases, the urine becomes scanty, the powers of life seem to yield, the lungs become œdematous, and, in a state of asphyxia or coma, he sinks into the grave; or a sudden effusion of serum into the glottis closes the passages of the air, and brings on a more sudden dissolution. Should he, however, have resumed the avocations of life, he is usually subject to constant recurrence of his symptoms; or again, almost dismissing the recollection of his ailment, he is suddenly seized with an acute attack of pericarditis, or with a still more acute attack of peritonitis, which without renewed warning, deprives him in eight and forty hours, of his life. Should he escape this danger likewise, other perils await him; his headaches have been observed to become more frequent; his stomach more deranged; his vision indistinct; his hearing depraved: he is suddenly seized with a convulsive fit, and becomes blind. He struggles through the attack; but again and again it returns; and before a day or a week has elapsed, worn out by convulsions, or overwhelmed by coma, the painful history of his disease is closed."

Acute Glomerular Nephritis

Ætiology

Infecting Organism. Acute glomerular nephritis follows infection with a β hæmolytic streptococcus, usually types 4 and 12, though a few other strains are occasionally involved. It is possible that the predilection of these strains to affect the kidneys is due to their having antigens in their cell walls which are the same as those in the basement membrane of the kidneys. This specificity of strain accounts for the irregular manner in which cases of acute glomerular nephritis appear. Until this was recognised, it was difficult to know why the incidence of acute glomerular nephritis varied so widely among epidemics of streptococcal infection: particularly why several members of a family should suddenly develop the disease almost simultaneously.

Site of Infection. This is usually the throat or the skin. Typically there is such a severe sore throat that the patient has to retire to bed for several days; in children, scarlet fever was at one time a major cause of acute nephritis, but it is now less frequent, probably because of the use of penicillin. The proportion of cases in whom it is possible to obtain a satisfactory history of previous infection is about the same in children as adults.

Interval between Infection and Onset. This interval varies from 2–3 days to more than a month; it averages 14 days. It is usual for the patient to have returned to work or school before the onset of acute glomerular nephritis

Sex and Age Acute glomerular nephritis is more common in males and is seen most often below the age of 20 years, however it is by no *means confined to this age group and is frequently seen at all ages* including the elderly

Abnormal Antigen-Antibody Response The theory for an immune basis in glomerular nephritis was suggested many years ago to explain the latent period of 10-21 days between an infection with scarlet fever and the development of acute glomerular nephritis The interval between the onset of renal disease and a preceding infection suggested that the former is not due to a direct infection of the kidneys with bacteria or bacterial toxins but that it takes time for the patient to become hypersensitive (i e to produce antibody) In addition bacteria have not been isolated from the kidneys of affected patients the lesions of glomerular nephritis cannot be produced by injections of streptococcal toxin and there is no relation between the severity of the human acute glomerular nephritis and the previous infection Other evidence for an immune response in human glomerular nephritis is provided by the decreased serum complement titre and the abnormal and persistent rise in plasma antistreptolysin titre in acute glomerular nephritis There is also the fact that gamma globulins and complement can be demonstrated in the glomerular lesions of both human and experimental glomerular nephritis As it is known that antibodies are present in gamma globulins thus finding suggests that antigen antibody complexes are fixed in the glomeruli The presence of complement in the glomeruli probably explains the low serum complement in acute glomerular nephritis

When considering hypersensitivity reactions it is necessary to differentiate between those in which antibody is transferred in serum (circulating antibodies) as in anaphylaxis and those in which it is transferred by lymphocytes as in homograft and tuberculin reactions Evidence for the presence of circulating antibodies against kidney in human glomerular nephritis is conflicting Though such antibodies have been identified on many occasions in both acute and persistent glomerular nephritis they have also been found in acute disease not associated with renal damage (e g acute rheumatic fever and infectious diseases)

There is thus some circumstantial evidence of an immune process in human glomerular nephritis though evidence for the presence of circulating anti kidney antibodies is confusing It is possible that this is because antibodies are present in such small quantities that they are difficult to detect by the methods available or that they have been

The first lesion to resolve is the diffuse endothelial proliferation. But focal areas of mesangial proliferation remain for a considerable time thereafter, even in those patients who eventually make a complete recovery. These focal collections lie along the stalks of the glomeruli and are particlarly noticeable at the periphery of the stalk. A peripheral lesion of this kind then consists of a collection of mesangial cell nuclei surrounded by a relatively large common " cytoplasmic " mass in which no cell boundaries can be discerned. Around the periphery of this lesion there lies a group of capillaries with normal walls. This residual focal mesangial proliferation is stated to be characteristic only of post-streptococcal nephritis.

The " cytoplasmic " mass which surrounds the proliferated mesangial cells is composed mainly of mucopolysaccharide which has been secreted in excess by mesangial cells in response to the inflammatory stimulus. The term " lobular stalk thickening " has been coined to describe the appearances produced when this material is deposited along the long axis of the glomerular stalk.

Clinical Features

The clinical features of acute glomerular nephritis are those of an acute nephritic syndrome (p. 190). Clinically the cardinal points are the sudden onset of œdema, gain in weight and oliguria; raised blood pressure and bradycardia; raised jugular venous pressure and dyspnœa; hæmaturia, proteinuria and discoloured urine. Acute glomerular nephritis is the commonest cause of " heart failure " in children. It is important not to be confused by finding that in most patients there is a high white cell excretion rate, and in about a third of patients an asymtomatic persistent bacilluria. The white cells presumably come from the acute inflammatory lesions in the kidneys which are themselves due to the deposition of antigen etc. The organisms responsible for the bacilluria are ordinary urinary pathogens such as *E. coli*; their relevance, if any, to the primary renal lesion is unknown.

Relationship Between Certain Clinical and Structural Features

Renal biopsy studies have shown that in acute glomerular nephritis the presence of proteinuria and hæmaturia is evidence of widespread and pronounced proliferative and inflammatory changes in the glomerular tufts, though the severity of these structural changes bears no relation to the extent of the proteinuria or hæmaturia. Surprisingly, there is only an uncertain relationship between the creatinine clearance and the structural changes in the glomeruli; and the concentration of the blood urea is the poorest guide to the presence or extent of such changes. Impairment in the ability to concentrate is certain evidence of widespread focal degenerative lesions of the tubules though these can be present without gross changes in concentrating ability a raised erythrocyte sedimentation rate above 50 mm in the first hour (Westergren) is highly suggestive of tubular degeneration Widespread necrosis of glomeruli is always associated with acute renal failure but otherwise there is little correlation between the presence of acute renal failure and the severity of the structural lesions

Course

In some series in children there have been no deaths and complete recovery in almost 100 per cent In adults complete recovery occurs in approximately 80 per cent of patients 5 per cent die within one or two weeks of acute pulmonary œdema renal failure or hypertensive encephalopathy while the remainder develop persistent glomerular nephritis The persistent stage may either develop as a rapid deterioration of the acute phase with increasing renal failure œdema and hypertension and death within a year (5 per cent) or there may be almost complete recovery except for the continued presence of proteinuria which persists for up to 25 years before the onset of chronic renal failure (10 per cent) A superimposed nephrotic syndrome occurs particularly in those who develop and die of persistent glomerular nephritis within a year

Differential Diagnosis

The onset of acute glomerular nephritis is sometimes indistinguishable from that of several other conditions which give rise to an acute nephritic syndrome The history of recent infection the identification of the streptococcus an antistreptolysin titre greater than 1 in 300 and the low level of serum complement are useful distinguishing points Occasionally a patient may present with acute renal failure following the use of a sulphonamide for a streptococcal infection It may then be extremely difficult to decide whether the patient has acute glomerular nephritis or acute tubular necrosis In such cases it is essential that the ureters be catheterised to make certain that they are not plugged with crystals of sulphonamide and tubular débris (p 154)

The two conditions which cause most confusion are some cases of polyarteritis nodosa and disseminated lupus erythematosus often the correct diagnosis is only made retrospectively A pyrexia for longer than the first two to three days or the continued presence of macroscopic hæmaturia are highly suggestive of a diagnosis of polyarteritis nodosa

Prognosis

At the beginning, acute renal failure is the complication most likely to destroy the patient. Acute glomerular nephritis is one of those rare causes of acute renal failure in which there is often complete cessation of urine flow. In adults acute renal failure due to acute glomerular nephritis nearly always causes death even if life is prolonged by appropriate measures. In children, however, dialysis is accompanied by recovery in most cases. Acute pulmonary œdema and hypertensive encephalopathy should respond to treatment whatever the age of the patient.

Recurrent exacerbations of hæmaturia and hypertension, with violent fluctuations in glomerular filtration rate and blood urea, carry an increasing risk that the patient may develop rapidly progressive persistent glomerular nephritis. Nevertheless a guarded prognosis should be given for a considerable time, for recovery may take place even if the disease has persisted in this manner for several weeks. It has been claimed that rapidly progressive glomerular nephritis never follows an attack of acute glomerular nephritis due to an infection with β hæmolytic streptococci. If the onset of acute glomerular nephritis is associated with a petechial rash, complete recovery is unusual.

The proteinuria which follows any attack of acute glomerular nephritis constitutes the most difficult prognostic problem. It is generally considered that the patient has an active renal lesion until proteinuria ceases, and that the longer this continues the more likely it is that he will develop persistent glomerular nephritis and renal failure. Complete recovery, therefore, has not taken place until proteinuria ceases. But for how long may it continue and yet recovery occur? Fig. 20.2, drawn from Addis's observations, gives the most comprehensive answer. It can be seen that whereas in the majority proteinuria ceases within two years, there are some patients in whom it continues for six to ten years before it disappears. The moral is to be optimistic.

Treatment

Prophylactic. It is reasonable to try and eradicate the β hæmolytic streptococcus from a small community (i.e. a family), in which a case of acute glomerular nephritis has occurred. The organism is highly sensitive and easily removed by one injection of long-acting penicillin.

Curative. There is no known way of preventing acute glomerular nephritis developing into persistent glomerular nephritis. Accordingly, treatment is directed solely at saving the patient's life and shortening the duration of the acute attack.

An attempt should be made to isolate the β hæmolytic streptococci immediately on the day of admission. Penicillin administration is begun on the same day and continued for a considerable time thereafter. Opinions differ, but some authorities consider that penicillin should be continued until proteinuria disappears, however long that may be.

Bed rest is essential, for it is remarkable how often a diuresis and recovery will begin within a few hours of the patient's retiring to bed, irrespective of the duration of the illness up to that time. Rest in bed also diminishes the risk of acute pulmonary œdema and hypertensive crises. For the first 24 hours it is well to allow only 500 ml. of sweetened fruit juice by mouth and nothing else. This allows time to observe the direction the illness is taking and its severity. If during that time a *diuresis has begun, i.e. if the urine volume is greater than 1,000 ml. and* there has been a loss of weight, then a normal diet and unrestricted intake of fluids is allowed. If a diuresis has not begun but the urine volume is greater than 400 ml., the intake of fluids for the next 24 hours should be limited to 500 ml. plus a volume equal to that which has been passed in the preceding 24 hours, a low salt, low protein diet is also started. By these means it is hoped to prevent the onset of acute pulmonary œdema and to minimise the rise in blood urea. If the urine volume has been *lower than 400 ml. the patient is considered to have* acute renal failure and treated accordingly (p. 153).

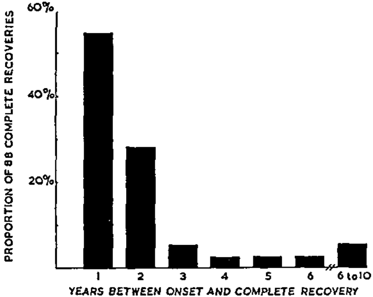

FIG. 20.2. Interval between onset and healing of acute glomerular nephritis in 88 cases who recovered completely. (After Addis 1949.)

The treatment of acute pulmonary œdema and hypertensive fits has been described on p. 193.

Once a diuresis has begun there is no evidence that the speed of recovery thereafter is influenced by the amount of protein in the diet. For instance, it has been shown that the duration of proteinuria following acute glomerular nephritis is the same whether abnormally high or low protein diets are given for some weeks after the oliguria and urea retention have ceased.

How long the patient should remain in bed once the œdema, the raised jugular venous pressure, hypertension and raised blood urea have disappeared is determined by the number of red cells or the amount of protein being excreted in the urine. Progress is best guided by the red cell excretion. The aim is to allow the patient to get up once the red cell excretion, *though still raised*, has reached a relative plateau. The excretory rate should have fallen to somewhere near 1,000,000/hr. Usually, however, progress is judged by the extent of the proteinuria, and again it should reach a steady level before the patient is allowed to get up. As a rough approximation, it should fall below 1 g./24 hours, or be no greater than + in a sample of urine with specific gravity above 1·016.

It is clearly a useless and an unwarrantable interference with the patient's liberty to keep him in bed until proteinuria disappears, for (1) proteinuria will persist for over a year in about half of the 90 per cent of patients who eventually make a complete recovery (Fig. 20.2), and (2) in those in whom the disease remains active it may persist as the only abnormality for 25 years. There is no evidence that the duration of rest in bed influences the eventual course of the disease.

Persistent Glomerular Nephritis

Ætiology

Clinically, persistent glomerular nephritis either (1) follows an attack of acute glomerular nephritis in a clinically recognisable manner, or (2) it presents without any previous known history or evidence of renal disease. In the first group it seems reasonable to venture that the development of chronic glomerular nephritis is related in some way to an abnormal antigen-antibody response to the β hæmolytic streptococcus, though there may be no evidence of such an abnormality by the time persistent glomerular nephritis develops. The ætiology of the second group is even more uncertain.

Presenting Renal Syndromes

Persistent glomerular nephritis may present as a rapidly progressive renal failure, a persistent proteinuria, recurrent hæmaturia (usually with persistent proteinuria), a nephrotic syndrome, or chronic renal failure

Pathology

The structural changes which occur with the rapidly progressive form of persistent glomerular nephritis are fairly exclusive The changes in the other clinical forms of persistent glomerular nephritis are only poorly related to the accompanying clinical features

Macroscopical Appearances in Persistent Glomerular Nephritis

The rapidly progressive form of persistent glomerular nephritis causes death within one or two years At autopsy it is unusual for

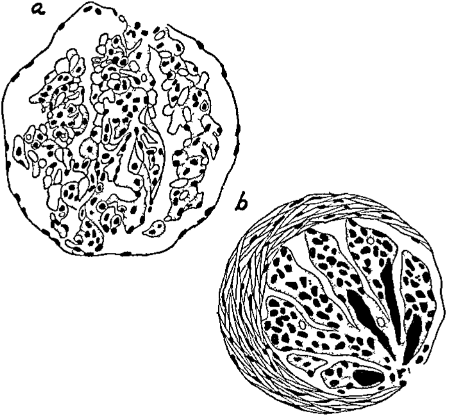

FIG 20 3 Persistent glomerular nephritis Schema of (a) normal glomerulus and (b) glomerulus in the rapidly progressive form of persistent glomerular nephritis The diagram accentuates the following points the capsular crescent the lobulation of the glomerular tuft the accumulation of eosin staining material (depicted as solid black clumps) and in addition some of the features of acute glomerular nephritis such as focal proliferation of cells polymorphs and narrow capillary lumens are shown there to be more than some cortical narrowing to be seen with the naked eye. The macroscopical appearances of the kidney in patients dying during a nephrotic syndrome may either resemble those found in patients dying of persistent glomerular nephritis with chronic renal failure, or both kidneys are pale, smooth and enlarged. Death from chronic renal failure is associated with bilateral, symmetrical, shrunken; irregular and firm kidneys, the surfaces of which are pitted from contraction of underlying fibrous tissue, and raised by areas of hypertrophied nephrons.

MICROSCOPICAL CHANGES IN THE RAPIDLY PROGRESSIVE FORM OF PERSISTENT GLOMERULAR NEPHRITIS

In the glomeruli the outstanding feature is one of intense widespread proliferation. This is most marked, as in acute glomerular nephritis, in the endothelial and mesangial cells, but the epithelial cells of the glomerular tuft also proliferate and swell. The distinguishing feature is the extensive proliferation of the cells of Bowman's capsule with the formation of numerous large, thick crescents (Fig. 20.3). Often these are so wide that they seem to compress and obliterate the tuft. The capillary wall changes are similar to but more pronounced than those found in acute glomerular nephritis. Some glomeruli are replaced by collagen. The tubules are invariably widely separated by a marked increase of interstitial material which is heavily infiltrated with chronic inflammatory cells. As in acute glomerular nephritis there are scattered foci of tubular necrosis.

MICROSCOPICAL CHANGES IN PERSISTENT GLOMERULAR NEPHRITIS PRESENTING WITH EITHER PERSISTENT PROTEINURIA, RECURRENT HÆMATURIA, A NEPHROTIC SYNDROME OR CHRONIC RENAL FAILURE.

With few exceptions patients with these clinical forms of persistent glomerular nephritis will have one of the following patterns of histological changes. (*a*) Proliferative changes in the glomerular tufts, sometimes with extensive tubular and interstitial involvement. (*b*) Changes in capillary walls of the glomerular tufts with little or no evidence of proliferation in the tufts and little or no tubular involvement. (*c*) No obvious glomerular lesion on light microscopy.

(*a*) *Proliferative Changes.* In the main these have been described in the section on acute glomerular nephritis (p. 237) for the changes are the same as those which follow soon after the acute phase. The extent of the endothelial and mesangial cell proliferation and the size and distribution of the deposits of mucopolysaccharide vary from patient to patient and within the glomeruli of any one patient. Capsular crescents are few in number but collagen replacement of glomeruli may be pronounced. Tubular changes may be minimal or there may be a generalised increase in interstitial tissue including varying amounts of fibrous tissue and extensive infiltration with cronic inflammatory cells.

Terminally the normal structural layout of the kidney is completely shattered (Fig 20.4). In the acute and rapidly progressive forms of glomerular nephritis there are severe changes, but the kidney continues to look like a kidney. After several years of nephron destruction it is hardly recognisable. There is a large amount of fibrous tissue interspersed with nephrons which are either hypertrophied or in varying stages of disintegration. One of the most striking features is the scarcity of glomeruli. Most of the tubules which remain are insignificant, atrophic and have flattened epithelium, and narrow lumens. Hypertrophied nephrons are easily identified by their large glomeruli and exceedingly wide tubules; it is in these large nephrons that the "broad" casts of chronic renal failure originate.

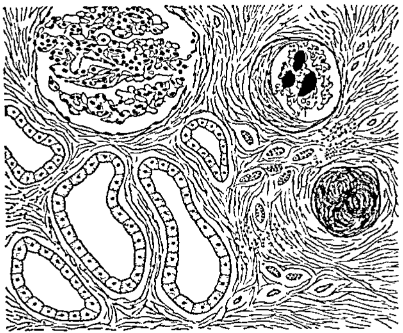

Fig. 20.4. Schema of persistent glomerular nephritis with chronic renal failure The diagram emphasises the following points the gross generalised disturbance with a hypertrophied glomerulus and tubule, surrounded by a matting of connective and fibrous tissue in which are embedded atrophic tubules, disintegrating glomeruli and some chronic inflammatory cells One glomerulus is completely fibrosed (depicted as solid black) while the third shows a crescent and deposits of an eosin staining material in the tuft.[1]

(*b*) "*Membranous*" *Changes.* The only change in some patients may be a thickening of the glomerular capillary walls (Fig. 20.5), and some swelling of the epithelial cells. In contrast to the capillary wall changes which have been described above in association with endothelial proliferation in acute glomerular nephritis, the thickening does *not* consist of a shredding of the luminal side of the membrane. Instead the thickening is fairly uniform and compact so that the capillary walls appear dense, and sharp in outline. With the electron microscope it is seen that the thickening of the capillary wall is mainly due to the fact that the epithelial cell foot processes have disappeared and instead the epithelial cell cytoplasm has increased in amount and now lies as an uneven layer on the surface of the basement membrane. There may

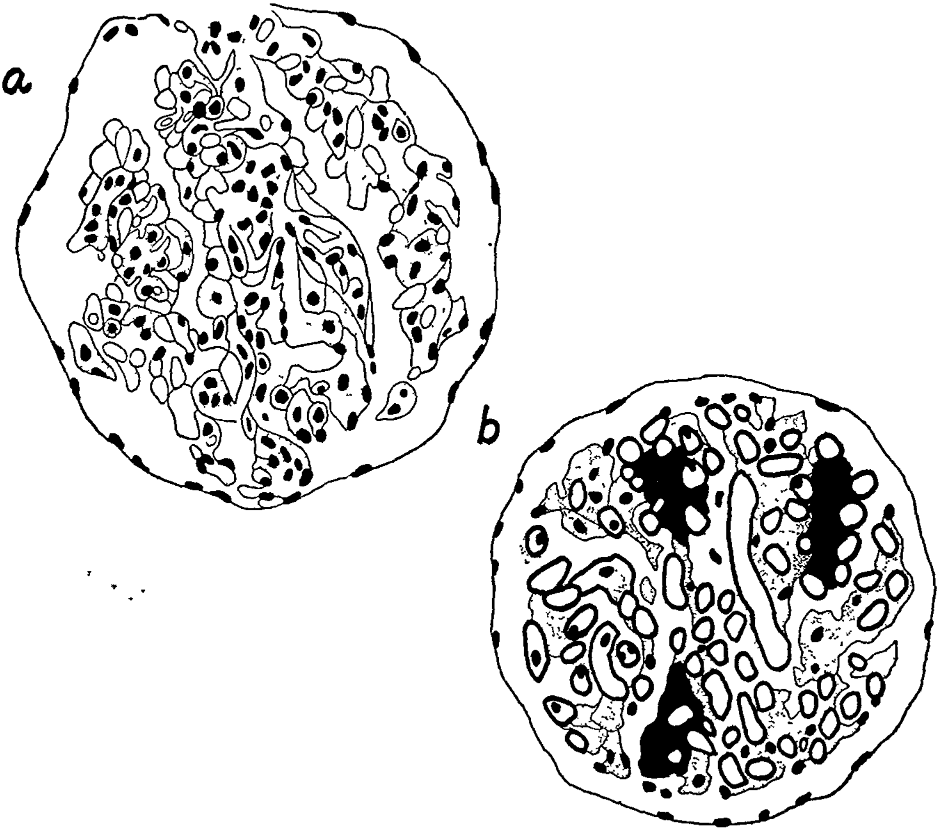

FIG. 20.5. Persistent glomerular nephritis; pure membranous change. Schema of (*a*) normal glomerulus, and (*b*) glomerulus in persistent glomerular nephritis. The diagram accentuates the following points: the increased thickness of the capillary walls; the deposits of eosin staining material (depicted as solid black clumps); and the relative paucity and smallness of the tuft nuclei.

also be focal deposits of some dense material between the basement membrane and the epithelial cell cytoplasm The basement membrane is often unchanged while in some patients it may only show areas of focal thickening and discrete collections of electron-dense material The term "membranous nephritis" dates from the time before electron microscopy, when it was thought that the even smooth thickening of the capillary walls was due to an even thickening of the basement membrane

(*c*) *No Glomerular Lesions on Light Microscopy* Some patients may have proteinuria but no glomerular lesions on light microscopy In nearly all such patients the electron microscope will reveal changes in epithelial cell foot processes similar to those described under (*b*) and the deposition of electron dense material in focal areas near or in the basement membrane

In all varieties of persistent glomerular nephritis there may be changes in the arteries, including atheroma, intimal and medial thickening, endarteritis obliterans and arteriolor necroses These in turn will produce varying degrees of change in the renal parenchyma (p 113) in addition to those just described

There is increasing evidence from serial biopsies in individual patients that the histological appearances in the glomeruli rarely change from one variety to another i e a patient with no definite abnormality or "membranous" change will not subsequently develop 'proliferative' changes and vice versa This is in contrast to the tubules which may suddenly become severely affected having previously been intact

Clinical Features

Persistent glomerular nephritis may make itself manifest at any age and occurs mainly in males

Rapidly Progressive Form of Persistent Glomerular Nephritis

This variety of glomerular nephritis often begins abruptly with an acute nephritic syndrome (p 190) or it may develop insidiously Some authorities state that it never follows an acute nephritic syndrome due to β hæmolytic streptococcal infection When it is a sequel to an acute nephritic syndrome there is often an initial diuresis and the signs of pulmonary œdema usually diminish or disappear, but the patient remains severely ill with lassitude, headache and malaise. Some œdema remains and there is much pallor The blood pressure remains raised and tends to continue rising the erythrocyte sedimentation rate is considerably raised and there is a persistent anæmia Glomerular filtration rate and blood urea fluctuate, but both gradually deteriorate, the ability to concentrate is always grossly impaired from the beginning

Proteinuria may increase greatly and a nephrotic syndrome often develops after a few weeks. Urinary red cell excretion is always raised to extremely high levels, from time to time there may be macroscopical hæmaturia.

When the condition develops insidiously, the patient presents because of increasing lethargy, malaise and headache. The signs and symptoms are those just described except that there is no evidence of pulmonary œdema.

Relationship between Clinical and Structural Features. Renal biopsy and autopsy findings have demonstrated that there is a fairly constant relationship between the clinical syndrome associated with the rapidly progressive form of persistent glomerular nephritis and the structural changes. Nevertheless, the histological changes give little information about the extent of functional impairment. For instance, it is impossible, from a histological picture, to distinguish those patients who have a nephrotic syndrome and a blood urea of less than 100 mg. per 100 ml. from those who have died of renal failure. On the other hand, the gross inability to concentrate the urine correlates well with the extensive tubular and interstitial lesions.

Course. Death occurs within 18 months of the onset of symptoms and is usually due to renal failure and severe hypertension.

Differential Diagnosis. Polyarteritis and disseminated lupus erythematosus are the two conditions with which the rapidly progressive form of persistent glomerular nephritis may be most often confused. Occasionally when the onset is gradual and the patient is middle-aged or older the condition may have to be distinguished from subacute endocarditis, amyloid disease or myelomatosis. A renal biopsy may be the only way to make certain of the diagnosis.

Treatment. There is no effective treatment. Prednisone usually makes things worse. In the past few years there have been certain claims that cytotoxic drugs can arrest the disease and even cause the proteinuria to disappear. As there have been no controls these claims have not been accepted, the criticism being that the good results are due to the inclusion of patients who were not primarily suffering from rapidly progressive glomerular nephritis.

Persistent Proteinuria of Persistent Glomerular Nephritis

Persistent proteinuria as the only abnormal clinical feature may follow a clinically recognisable attack of acute glomerular nephritis, but more frequently it does not do so. It is usually discovered on routine investigation. At first it may be the only indication of the presence of glomerular nephritis. Later a nephrotic syndrome may develop, or chronic renal failure and hypertension, or there may be a

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sudden exacerbation with a superimposed acute nephritic syndrome Often the proteinuria is accompanied by a fluctuating increase in red cell excretion

Relationship between the Clinical and Structural Features The most striking finding is that this symptomless proteinuria in an otherwise healthy person may be associated with any of the wide variety of those histological abnormalities which distinguish glomerular nephritis These may be identifiable only with an electron microscope, or there may be a smooth dense thickening of the basement membrane, or extensive proliferation with much tubular and interstitial damage. It is also remarkable that the histological appearances are no guide to the probable duration of survival

Course and Prognosis These are more easily considered with the chronic renal failure of persistent glomerular nephritis (p 255)

Differential Diagnosis As nearly all renal disease presents with proteinuria the differential diagnosis is a wide one The first step is to exclude orthostatic proteinuria Subsequently an extensive investigation is necessary, including an I V P, renal biopsy, urinary cell excretion rate, creatinine clearance, and the ability to concentrate and to acidify.

Treatment There is no known treatment A control trial on the use of cytotoxic drugs is badly needed

Recurrent Hæmaturia of Persistent Glomerular Nephritis

This form of persistent glomerular nephritis is sometimes known as recurrent "focal" nephritis It occurs almost exclusively in young or adolescent males Often each attack is associated with a sore throat or "cold" and a general feeling of malaise out of proportion to the upper respiratory symptoms These are not due to infection with β hæmolytic streptococci, it has been claimed, but not proven, that a virus is sometimes responsible Hæmaturia begins at the same time or within one to three days of the onset of sore throat and it may last several weeks As it settles the patient's general symptoms also improve. During the attack there may be some transient mild impairment of renal function but no œdema or hypertension In between the attacks the patient feels well Eventually most patients have persistent proteinuria though it may not become persistent until they have had several relapses A raised urinary red cell excretion accompanies the persistent proteinuria

Relationship between Clinical and Structural Features The microscopical appearances are either normal or there may be endothelial proliferation in the glomeruli with the tubular and intestinal lesions described above Sometimes in the milder cases the lesions may be remarkably scattered, and it is for this reason that the term " focal " nephritis was originally used. The relation between these structural changes and subsequent progress is not known for only few patients who have had a renal biopsy have been followed for a sufficiently long time. In general, those with the most advanced changes tend to continue to have frequent attacks.

Course and Prognosis. It was originally considered that when hæmaturia and a sore throat developed simultaneously the renal condition was benign and transient. It is probable that with a single episode this is a justifiable conclusion. When there are recurrent attacks, however, the long-term prognosis is not so good. Some patients have been known to have recurrent attacks for 25 years without any marked deterioration. But many others with perhaps more frequent attacks eventually die of renal failure and hypertension. There is an unknown number in whom the attacks cease and who appear to make a full recovery. As in all immunological diseases of the kidney children have the best prognosis and often do well even though they have multiple attacks.

Differential Diagnosis. This syndrome is quite easily separated clinically and histologically from the rapidly progressive form of persistent glomerular nephritis or acute glomerular nephritis. The combination of recurrent painless hæmaturia and a sore throat should exclude local structural conditions of the kidney though the condition has been confused with recurrent pyelonephritis or renal stones. The first attack is the most difficult to distinguish with any certainty. It can easily be confused with the onset of polyarteritis nodosa, or some " bleeding " disorder including Henoch-Schonlein's purpura.

Treatment. There is no consistently effective treatment. It seems reasonable to keep the patient in bed until he feels better, and it is convenient that the duration of this period usually coincides with the duration of macroscopic hæmaturia. Some authorities give prophylactic oral penicillin to avoid a superimposed β hæmolytic streptococcal infection. In some patients prednisone may produce a quick remission, but in others it only makes things worse. A control trial of cytotoxic drugs, in those patients who have repeated attacks, is needed.

Nephrotic Syndrome of Persistent Glomerular Nephritis

The clinical features of a nephrotic syndrome have been described on p. 126. It is usual for the onset to be gradual, but a rapid onset sometimes occurs.

Relationship between the Clinical and Structural Features. These are the same as in those patients with persistent glomerular nephritis who present only with persistent proteinuria. In the individual case the histological appearances are little guide to the probable duration of survival, though in general the prognosis is better when the structural changes are minimal, this is particularly evident in children

The extent of the proteinuria bears hardly any relation to any recognisable light microscopy change in the glomerulus except that (1) occasionally a patient passing very large amounts of protein may have a foamy distention of some of the glomerular cells, as if they were distended with some fatty substance, and (2) within wide limits the quantity of protein excreted diminishes as the number of functioning glomeruli become less, i e with a low glomerular filtration rate less protein is filtered and excreted The relation between the " selectivity " of the proteinuria and the histological appearances has been described on p 129

The loss of epithelial cell foot processes, however, does seem to occur only with extensive proteinuria, and it has been demonstrated both in man and in experimental animals that if the proteinuria diminishes the foot processes re form

Course and Prognosis Before the introduction of antibiotics, secondary infections were the commonest cause of death, and the natural course of the disease was obscure Now that infection is a rare cause of death a clearer picture is emerging, but it will take several decades before an accurate appraisal is available Meanwhile it continues to be difficult to interpret published findings because of differences in terminology A diminishing number of authorities, particularly among those who look after children, consider that when a nephrotic syndrome is not associated with hæmaturia, hypertension, or a reduced glomerular filtration rate, it is a separate entity unrelated to glomerular nephritis, and they distinguish it by the term " pure or genuine nephrosis "

Some 30–50 per cent of cases will develop renal failure and/or hypertensive cardiac failure, and die within a few years of the onset, about 20–50 per cent will recover completely, perhaps after several remissions and relapses, and a few (? 5 per cent) will also have complete remission but will continue to have irregularly spaced relapses until proteinuria becomes permanent, when they join the group of 20–40 per cent who continue to have œdema and proteinuria of varying severity for many years (up to 30 years) before developing renal failure and/or hypertensive cardiac failure Generalised œdema usually persists even when renal failure is advanced and proteinuria has diminished An exacerbation or relapse of œdema and proteinuria is sometimes heralded by the onset of an acute nephritic syndrome Complete recovery becomes less likely the longer the duration of the disease

As death is due either to renal failure or hypertension it is clear that as long as there is no evidence of either, the immediate and short term prognosis is good. But even when these ominous signs do appear the prognosis is not necessarily poor, for sometimes, after an anxious few weeks, renal function may improve, hæmaturia cease, and the blood pressure return to normal. Occasionally the glomerular filtration rate may remain around 40–60 ml./min. and the blood urea 50–70 mg. per 100 ml. for many years even though there may be intermittent periods of transient deterioration (in two cases up to 20 years). In some instances the blood pressure rises gradually but there is no marked deterioration in renal function.

The earlier in the disease that hypertension and renal failure occur the worse the prognosis, particularly in children; it is also a bad sign when the extent of the œdema is massive and is difficult to remove.

Differential Diagnosis. The other conditions in which the nephrotic syndrome may appear are given on p. 133. Cases due to myelomatosis diabetes, anaphylactoid purpura or irradiation of the kidneys are easy to distinguish. An important cause which must always be kept in mind is the administration of troxidone. Amyloid disease of the kidney may be inferred from the clinical history and confirmed by biopsy; occasionally a renal biopsy shows amyloidosis when the clinical history is unhelpful or misleading and a liver biopsy negative. Thrombosis of the renal vein is suspected if there is evidence of inferior vena caval thrombosis, recurrent pulmonary emboli from the unknown site, or the patient is known to have only one kidney, or amyloidosis.

There remain polyarteritis and disseminated lupus erythematosus (D.L.E.). Polyarteritis as a cause of the nephrotic syndrome is unusual; at the onset it may be very difficult to distinguish from glomerular nephritis; renal biopsy is rarely helpful. The diagnosis is made when some more characteristic features of polyarteritis nodosa become evident (peripheral neuritis, fever, tachycardia, muscle pains, etc.) and is confirmed by muscle biopsy. D.L.E. is the most difficult condition to distinguish from glomerular nephritis, for sometimes there are no firm clinical reasons for suspecting it and renal biopsy findings may be equivocal. The only distinguishing feature may be the presence of L.E. cells in the peripheral blood or bone marrow, and antinuclear factor in the peripheral blood.

Treatment. The treatment of nephrotic glomerular nephritis is mainly symptomatic. It is particularly concerned with the elimination of œdema by a variety of methods, all of which have been discussed on p. 132. Prednisone is used in children (p. 133) but the evidence that its long-term value is any greater than an effective diuretic is not available. This is unfortunate for a few children continue to die of the side effects of prednisone In adults the relative uselessness and obvious dangers of using steroids has been discussed on p 136 where the total lack of objective evidence on the efficacy of cytotoxic drugs is also mentioned Nevertheless in an individual patient with a nephrotic syndrome in whom there is a *rapid deterioration of renal function*, it is still ethically desirable (in the present state of our ignorance and lack of general agreement) that a course of prednisone should be given with the patient under observation in hospital It has been claimed that this may sometimes be associated with a rise in glomerular filtration rate and a fall in blood urea Usually however there will be no beneficial effect or an accelerated deterioration The dose of prednisone should then be lowered and a trial of a cytotoxic drug and prednisone can then be started As relapses and remissions frequently follow infections, particularly those in the respiratory tract reasonable attempts should be made to avoid these hazards and when they occur they should be treated promptly and energetically with antibiotics

Chronic Renal Failure of Persistent Glomerular Nephritis

The clinical features of chronic renal failure have been described on p 165 This is the final stage through which pass most patients who eventually succumb to persistent glomerular nephritis Though in a few cases it is already known that the patient suffers from persistent glomerular nephritis, in the majority the symptoms of advanced chronic renal failure, hypertensive cardiac failure, or malignant hypertension are the first indication of its presence

Relationship between the Histological and Structural Features The individual lesions are the same as those described in patients with persistent proteinuria, recurrent hæmaturia or the nephrotic syndrome The main difference is that the lesions are now more extensive, particularly those involving the tubules and interstitial spaces.

Renal function and the duration of survival are only poorly correlated with the extent of the histological findings

Course and Prognosis The rate of renal destruction varies very greatly it may fluctuate with quiescent periods and acute exacerbations The duration of the disease, from beginning to end may extend to 30 years, but, once the glomerular filtration rate has begun to fall and the blood urea to rise, there is a tendency for the advance of chronic renal failure to be fairly rapid and inexorable As a very rough approximation once the blood urea is greater than 50 mg per 100 ml. the prognosis is not likely to be greater than 3–5 years and over 100 mg per 100 ml. 1–2 years These figures relate to the concentration of blood urea when the patient is on an unrestricted diet, has not had a recent hæmorrhage or attack of diarrhœa and vomiting, is free from cardiac failure, and is not suffering from an acute exacerbation of the disease process as evidenced by the development of an acute nephritic syndrome or hæmaturia. It has already been stressed repeatedly how circulatory insufficiency exacerbates renal failure and tends to give an erroneous impression of the extent of any underlying renal structural damage. Such an exacerbation may cause death from acute renal failure at a time when there is only a moderate amount of renal structural damage.

In general, the higher the blood pressure the poorer the prognosis.

Differential Diagnosis. Unless there is a suggestive past history, it is almost impossible to clinch a diagnosis of persistent glomerular nephritis as a cause of chronic renal failure without a renal biopsy.

Persistent glomerular nephritis has to be distinguished from the other causes of chronic renal failure (p. 165). It is important that there should be no confusion with chronic renal failure due to *chronic urinary obstruction*; the distinction is not particularly difficult.

The most common causes of confusion are chronic pyelonephritis, and nephrosclerosis (i.e. renal destruction directly due to hypertension (p. 113).

In chronic pyelonephritis there are, in addition to persistent proteinuria, chronic renal failure and hypertension, the following signs and symptoms: (1) The urine contains organisms, though these may only appear intermittently, and in advanced chronic pyelonephritis the urine may always be sterile; (2) there may be a history of recurrent unexplained " chills," rigors and fevers, often with loin pains; (3) intravenous and retrograde pyelograms show scarring of the renal parenchyma with deformities of the renal calyces, the characteristic feature of which are their bizarre shape, and the way in which one side may be more severely affected than the other; (4) the urinary excretion of white cells is very large and usually greatly exceeds that of red cells.

In persistent glomerular nephritis the extent of the structural disturbance is the same on the two sides, and the urinary excretion of red cells is much greater than that of white cells. Frequently none of these points of difference is present and in advanced cases a renal biopsy no longer distinguishes the original disease.

The distinction between persistent glomerular nephritis and nephrosclerosis is often impossible without a renal biopsy. The urinary deposit in nephrosclerosis is characteristically small and consists of approximately equal numbers of red and white cells, but this is a tenuous point on which to base a diagnosis. Statistically the more severe the renal failure the more certain the diagnosis of persistent glomerular nephritis becomes, for " non-malignant " hypertension only rarely causes advanced renal failure Again, if a patient is found to have malignant hypertension and there is no previous history of renal disease, it may be impossible to determine whether there exists an underlying chronic structural lesion such as persistent glomerular nephritis. Malignant hypertension is more likely to be a complication of pre-existing renal disease if the kidneys are small (straight X ray of the abdomen or I V P), or the renal failure is advanced when the diagnosis is first made

Treatment is that of chronic renal failure (p 178) It aims at minimising or controlling certain functional impairments It is doubtful if any method slows the rate of renal structural disintegration, except the control of hypertension

RENAL POLYARTERITIS NODOSA

This disease produces generalised disturbances (such as fever), and focal vascular lesions, in about 80 per cent of cases the kidneys are involved, either alone or in combination with other organs

The ætiology of polyarteritis nodosa is unknown but, since gamma globulin and complement are found in the glomeruli and similar disturbances and lesions can be produced in animals by inducing certain antigen antibody reactions, it is probable that such a stimulus is responsible for the disease in man

Pathology

The characteristic vascular lesions in the kidney may occur in the glomerular capillaries, the arterioles, or the small and medium sized arteries In renal biopsies, however, the overall changes are difficult to distinguish from those of glomerular nephritis The arterial lesions are scattered and difficult to find

The characteristic glomerular lesion is a focal necrotising capillaritis in the midst of an acute inflammatory reaction occasionally the entire glomerulus is necrosed (Fig 20 6) The arterioles may either show arteriolar necrosis with perivascular inflammatory cell reaction, or endarteritis obliterans (i e the same lesions as in malignant hypertension, except for the perivascular inflammation) The medium and small sized arteries show the diagnostic lesion of polyarteritis nodosa, that is focal areas of acute segmental necrosis of a part or the whole of the arterial wall, together with an acute inflammatory reaction which invades and surrounds the necrotic area

All these lesions occlude the lumen of the affected vessels and therefore the changes in the renal parenchyma (and the clinical features) largely depend on which vessels are involved When the glomerular capillaries and the arterioles are affected the glomeruli show exudative and proliferative changes.

When the small and medium sized arteries are affected there will be wedge-shaped areas of infarction in which the glomeruli will at first only appear " coagulated " or " clumped " and then become fibrosed and structureless, while the tubules, particularly the proximal tubules, become atrophied at an early stage; relatively normal renal tissue may surround the infarcts.

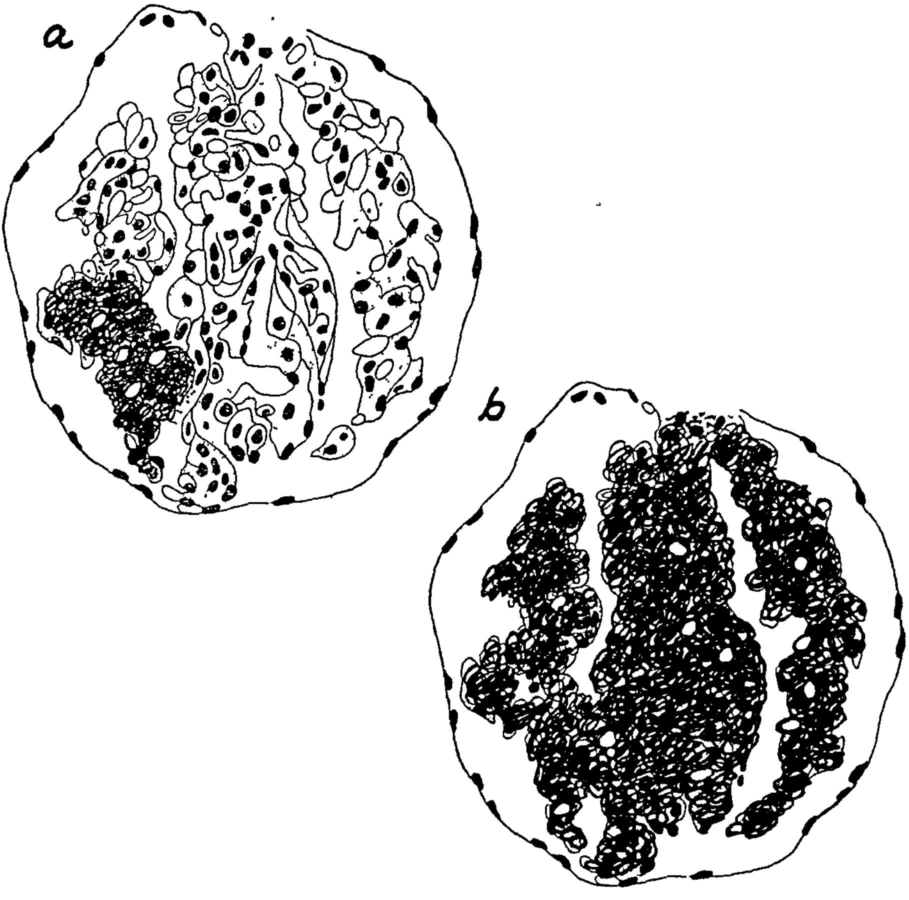

FIG. 20.6. Polyarteritis nodosa. Schema of two glomeruli; one (*a*) illustrates that the necrotic lesions may be focal while the other (*b*) shows that the whole glomerulus may become necrosed.

Sometimes when the larger vessels are affected, the glomeruli may appear relatively normal but there are widespread tubular changes throughout the renal parenchyma, including tubular separation, changes in the nuclei, flattening of the tubular cells, and increase in size of their lumens It is possible that these lesions are due to partial occlusions of the arcuate arteries

When the vascular lesions heal there are focal areas of marked intimal fibrosis which contain capillaries (the sites of recanalised thrombi), focal ruptures of the internal elastic lamina, and areas of focal fibrosis of the arterial walls extending into the surrounding tissues

Clinical Features

The wide variety of pathological changes accounts for the extensive range of clinical features Renal polyarteritis nodosa may present as *acute renal failure, chronic renal failure an acute nephritic syndrome* or a nephrotic syndrome, the predominant abnormality may be proteinuria or severe hæmaturia or tubular inability to control electrolyte excretion The blood pressure tends to rise after the renal symptoms have appeared, and may continue to rise until there is *malignant hypertension* *The disease is more common in men than* women and is more easily diagnosed in the young than in the elderly

Acute renal failure occurs if there are extensive necrotic lesions in the glomeruli, while proteinuria, chronic renal failure and severe hypertension are more likely if the lesions are in the small and medium sized arteries and there are *multiple infarcts*

One of the most frequent ways in which renal polyarteritis presents is as an acute nephritic syndrome For a few weeks the diagnosis is usually confused with acute glomerular nephritis, but eventually the slow rate of recovery, or the stormy course of the syndrome, together with the appearance of some other *non renal clinical feature of poly arteritis* nodosa, suggests the proper diagnosis There may be attacks of severe unexplained central abdominal pain, fever, tachycardia, leucocytosis and eosinophilia, peripheral neuritis, pulmonary symptoms and radiological opacities in the lungs skin rashes and nodules, or muscle pains and tenderness *The most characteristic features of* active renal polyarteritis are (1) recurrent, irregularly spaced, sharp attacks, of unremitting unilateral loin pain of sudden onset, usually lasting for less than an hour, and followed by an increased rate of red cell excretion in the urine, these probably occur at the moment of, or shortly after, the formation of *small renal infarcts, occasionally the* pain radiates to, or may be situated entirely in, the flanks and front of the abdomen, and (2) long continued excretion of fluctuating quantities of *macroscopic* hæmaturia

Finally the ability of the kidney to concentrate the urine is often *impaired to a far greater extent than is the glomerular filtration rate*

Course and Prognosis

Before the use of cortisone the majority of cases of renal polyarteritis nodosa died of renal failure or hypertensive cardiac failure within one or two years of the onset of the disease; the prognosis today is only a little better.

The natural clinical course is often one of remissions and relapses, and occasionally evidence of such fluctuations can be found at autopsy, when both healed and active lesions of polyarteritis are seen. At any moment acute activity may cease. Ultimate recovery then depends on the extent of the vascular lesions, for healed lesions may continue to produce harmful effects, such as malignant hypertension or chronic renal failure.

Death may occur from lesions in other sites, but renal failure is the commonest cause of death in polyarteritis. Many cases develop renal failure fairly rapidly and die within a few months; those who begin with acute renal failure die within a few days.

Nevertheless some cases do recover; their number is not known, for unless there is positive histological evidence the diagnosis is uncertain, and it is obvious that such evidence is obtained less often in those patients who recover than in those who succumb.

Differential Diagnosis

Syphilis used to be known as " the great imitator " because of its ability to mimic so many other diseases. Now that advanced syphilis is rarely seen, this title might well be transferred to polyarteritis nodosa.

The renal disturbances caused by polyarteritis may suggest almost any form of renal disease. Unfortunately renal biopsy is not of much help in diagnosis, for unless a necrosed arteriole or artery is seen, surrounded by an intense inflammatory reaction, the diagnosis remains in doubt; and the chance of finding such a lesion in the small amount of tissue removed by biopsy is remote. The other renal histological features of polyarteritis may also appear in glomerular nephritis, lupus erythematosus, " embolic nephritis," malignant hypertension, and anaphylactoid purpura.

A useful clinical point in difficult cases is the presence of fever, however mild it may be. If blood cultures are negative, there are no lupus erythematosus cells or autinuclear factor in the peripheral blood, and the urine is sterile, renal disease associated with a pyrexia is probably due to polyarteritis nodosa. When polyarteritis is responsible for a nephrotic syndrome it is characteristic that the 24-hour urinary excretion of protein and the decrease in plasma proteins is more moderate than the extent of the œdema would suggest. Intermittent cardiac failure of uncertain origin and associated with only mild *hypertension is another tenuous indication of polyarteritis*

Treatment

Adrenal steroids and ACTH are the only effective means of treatment They often produce a remarkable and immediate remission of the acute symptoms, and in some cases they indubitably prolong life The dose should be large (e g 40–100 mg prednisone per day), and it is essential that once a favourable effect has been produced the quantity should be continued uninterruptedly at a high level If the dose of adrenal steroid is lowered too rapidly there is often a relapse of symptoms, which for some inexplicable reason then no longer respond to adrenal steroids, or only do so when they are given in very large and potentially dangerous amounts (150 mg of prednisone per day) Treatment with adrenal steroids should be continued for at least a year, the dose being lowered very gradually at monthly intervals during that time (e g by 1–2 mg each month), if signs of activity persist treatment should be continued for longer

The complications of adrenal steroid therapy have been mentioned (p 136) The most important risk in the treatment of polyarteritis nodosa is retention and accumulation of salt and water, which may precipitate cardiac failure or a further rise in blood pressure Initially therefore it is essential to measure the patient's weight and blood pressure and observe his jugular venous pressure each day If necessary salt and water retention can be controlled by diuretics, and if the blood pressure begins to rise it should be lowered by hypotensive drugs In some cases in which the blood pressure is very high at the onset it may be advisable for it to be lowered before beginning treatment with adrenal steroids

RENAL LUPUS ERYTHEMATOSUS

Systematised lupus erythematosus resembles polyarteritis nodosa in that it also produces generalised disturbances and affects a wide variety of organs The ætiology of lupus erythematosus is unknown, it is highly probable that it is another form of abnormal antigen-antibody response Again gamma globulins and complement can be found fixed in the glomerular capillary walls

Pathology

Systematised lupus erythematosus may occur without any structural abnormality evident in the kidneys Patients with renal lesions may be divided into two groups, some who only have mild focal glomerular lesions, and the others who have more extensive glomerular lesions together with changes in the interstitial spaces and the tubules.*

The glomerular lesions include all those changes found in glomerular nephritis; proliferation, " membranous ", focal depositions of mucopolysaccharide and collagen, capsular crescents, and focal necrosis. The most characteristic lesion in the group in whom the renal changes only affect the glomeruli consists of scattered areas of endothelial proliferation of the glomerular tufts with focal thickening of capillary walls. On electron microscopy these areas may show focal areas of gross thickening of the basement membrane. During an acute flare-up of the disease cellular proliferation increases and there are focal patches of degeneration and necrosis. In some of these " hæmatoxylin " bodies may be found. These bodies represent breakdown products from disintegrating nuclei circulating in the peripheral blood; they appear as smudged hæmatoxylin-staining areas of varying size.

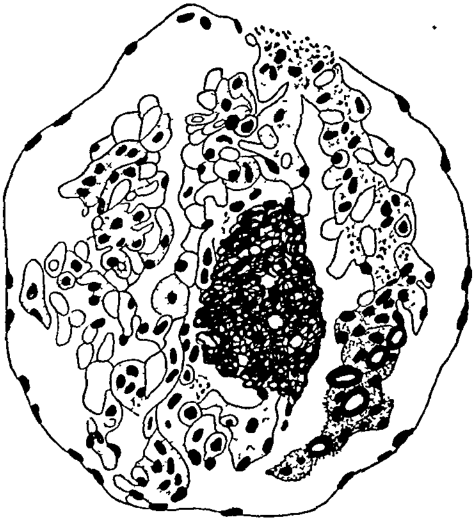

FIG. 20.7. Disseminated lupus erythematosus. Schema of a glomerulus in renal lupus erythematosus. The diagram accentuates the focal nature of the lesions and that these consist of necrosis (in the centre), and cellular hyperplasia together with gross thickening of the walls of a few capillaries (both in the lower right quadrant).

Acute exacerbations are also accompanied by focal changes affecting the whole of one or several contiguous glomerular capillary loops. The walls of these capillaries show such a gross thickening that they are sometimes known as " wire loop " lesions. This term is misleading, for it contains the implication that the thickening of the capillary walls that occurs in renal lupus erythematosus is easily distinguished from that which occurs in other conditions, which is not true The thickening is due to non specific changes which include (1) a granular disruption of the basement membrane, (2) an increase in basement membrane material, and (3) deposition of collagen The only features characteristic of lupus erythematosus are that the width and granularity of the capillary walls are *occasionally very pronounced, and that these gross* changes may be found in one part of the glomerulus, while the other parts are relatively normal (Fig 20 7) *Even these vague distinctions* however, are becoming less useful, for after the administration of *prednisone they occur much less frequently*

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* The term lupus glomerulitis is sometimes used to denote changes in the first group, and lupus glomerulonephritis the changes in the second.

The tubular and interstitial changes are the same as those found in a wide variety of renal diseases The tubules become separated from each other by a structureless material in which there are focal collections of inflammatory cells The tubules show various changes including focal necrosis, atrophy and dilatation

Death from renal failure may take place before there has been much disintegration and absorption of nephrons In such cases the kidneys macroscopically are of normal size or enlarged, while histologically there is a striking proliferation of both the glomerular capsule and the tufts, thickening and granularity of the capillary walls, exudates, hæmorrhages, and even necrosis in the tufts If on the other hand, the changes have occurred more slowly, particularly when they *have been retarded by prednisone, the kidneys will be smaller and the* histological changes will resemble more closely those of advanced glomerular nephritis

Vascular changes may not be particularly pronounced, though sometimes the lesions of polyarteritis nodosa, or fibrinoid necrosis of arterioles, may be present

Clinical Features

Renal lupus erythematosus presents as proteinuria, a nephrotic syndrome, chronic renal failure or occasionally as an acute nephritic syndrome

Proteinuria and a nephrotic syndrome are the two most frequent presentations Usually the correct diagnosis is not made until some other more characteristic features of lupus erythematosus become manifest, e g skin lesions, fever, pleural effusion, pericarditis, arthritis, leucopenia, high erythrocyte sedimentation rate, and " L E " cells in the blood or bone marrow or antinuclear factor in the blood Sometimes a patient may develop a nephrotic syndrome without a raised blood cholesterol

By the time chronic renal failure occurs the diagnosis is usually less difficult. It is characteristic that the blood pressure rises less frequently and much later than in other causes of renal failure, and that malignant hypertension is exceptional.

The disease is more common in women than in men.

Relation Between the Clinical and Structural Features

In keeping with most other renal diseases there is little correlation between the clinical picture and the histological changes, except that when there is some degree of renal failure there are lesions in the interstitium and tubules as well as in the glomeruli. But in the absence of renal failure, proteinuria may be present with either no histological abnormality, or with well defined lesions in both the glomeruli, and the interstitial space and the tubules.

Course and Prognosis

Follow-up studies with serial renal biopsies have shown that it is most unusual for patients with systematised lupus erythematosus who initially have no renal lesions to develop such lesions at a later date. Similarly, it is uncommon for a patient whose renal lesions are confined to the glomeruli to develop tubular and interstitial lesions subsequently, though it can happen.

The prognosis in patients who have no renal lesions or in whom these lesions are limited to the glomeruli is much better than in those in whom the lesions extend into the interstitial space and tubules. Persistent hypertension or renal failure with blood ureas greater than 100 mg./100 ml. also carries a poor prognosis, death occurring within a few years. Transient rises in blood pressure, however, during acute exacerbations of D.L.E. are not important. Patients with a nephrotic syndrome have a variable prognosis, some dying within one year while others have survived for up to 10 years.

In the absence of hypertension or renal failure, pregnancy does not appear to influence the progress of the disease.

Differential Diagnosis

The most diagnostic features of lupus erythematosus are the skin lesions, the presence of " L.E." cells in the blood and bone marrow and the presence of antinuclear factor in the blood. Without these it may be impossible to distinguish with certainty renal lupus erythematosus from other causes of renal disorder.

The conditions most likely to be confused with renal lupus erythematosus are renal polyarteritis nodosa, the nephrotic stage of glomerular nephritis and bacterial endocarditis.

Treatment

During an acute exacerbation of D L E in which there are large numbers of red cells in the urine, deteriorating renal function and lesions in the tubules and the interstitial space as well as in the glomeruli it is essential to give large quantities of steroids over a prolonged period, e g 40–60 mg /day for six months gradually reducing to 15 mg /day thereafter This will increase survival and reverse the structural lesions

It is doubtful if there is any need to give steroids if the patient is symptomless and the lesions are confined to the glomeruli Treatment of the nephrotic syndrome with steroids is uncertain but can be tried, while the results with cytotoxic drugs or chloroquine have been equivocal

It is important in all patients with D L E to try and avoid factors which may cause an acute exacerbation of the process, e g sunbathing drugs such as penicillin, certain cosmetics hair dyes and certain household and garden chemicals

RENAL DISTURBANCES IN SUB-ACUTE BACTERIAL ENDOCARDITIS

Renal disease due to sub acute bacterial endocarditis is also called " embolic " nephritis, on the assumption that the disturbance is due to multiple renal emboli There is, however, considerable doubt about this assumption, for

1 The lesions are rarely seen until the infection has been present for at least six weeks

2 Bacteria are almost never found in the kidney

3 When they are found it can be seen that the lesions they have provoked to not resemble the majority of the lesions which are present and which do not contain bacteria

4 In some instances there are large numbers of lesions in the kidney, and few in other parts of the body

5 The typical renal lesions can be produced experimentally as a feature of an abnormal antigen antibody response

6 Foreign particles injected into the circulation may embolise in the kidney but do not produce the characteristic lesions found in sub-acute bacterial endocarditis

These points suggest that the renal lesions in sub-acute bacterial endocarditis may be due principally to an abnormal antigen antibody response to the organism responsible for the infection in the heart

Pathology

Macroscopically the kidney may appear normal, but if a considerable number of glomeruli are undergoing acute changes it may be swollen and covered with numerous petechial hæmorrhages, as in acute glomerular nephritis, malignant hypertension and diffuse lupus erythematosus.

The characteristic microscopical lesion is an area of acute necrosis of a part (Fig. 20.8) or the whole of a glomerulus, surrounded by varying quantities of acute inflammatory cells, and in the midst of which there may be intracapillary thrombi. Occasionally there may also be arteriolar necrosis of afferent arterioles. These lesions are usually scattered in widely separated glomeruli, but they are sometimes present in the majority. They are identical to the changes seen in the glomeruli and afferent arterioles in polyarteritis nodosa; the difference between the two conditions being that in bacterial endocarditis the small and medium-sized arteries are not affected.

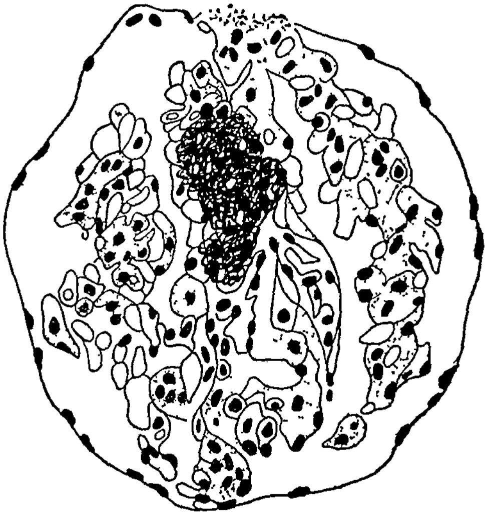

FIG. 20.8. Sub-acute bacterial endocarditis (embolic nephritis). Schema of the characteristic focal necrotic lesion in a glomerulus.

Following this acute stage the glomerular lesions become round structureless masses of eosin staining material and eventually become fibrosed. Characteristically these circular collections can be seen within otherwise normal glomeruli.

Patients who have died from renal failure usually show, in addition, the lesions of acute or persistent glomerular nephritis.

Clinical Features

Frequently the patient is thought, or known to be suffering from sub-acute bacterial endocarditis, and routine examination of the urine shows occasional showers of red cells, or frank hæmaturia; such findings then help to establish the correct diagnosis.

Sometimes the diagnosis of endocarditis has not been considered or has been rejected because pyrexia and cardiac murmurs have been absent, or repeated blood cultures have been sterile In these patients the significance of the proteinuria and the excretion of a few red cells may not be properly appreciated This occurs particularly in the elderly, who may then develop fatal renal failure

In early cases treatment of the infection successfully prevents the further development of renal disturbances, but in cases with advanced renal failure such treatment is unlikely to save life.

Diagnosis

A positive blood culture settles the diagnosis

When blood cultures are sterile, a renal biopsy may be helpful

Treatment

This consists in identifying the organism, determining its sensitivity to various antibiotics and then giving the appropriate one in suitable doses for a period of six weeks or longer, depending on when the blood cultures become sterile

RENAL DISTURBANCES IN ANAPHYLACTOID PURPURA

Anaphylactoid purpura (the Schonlein Henoch syndrome) is characterised by a purpuric rash, abdominal pains polyarthritis and hæmaturia, these usually occur in the young and follow a well-recognised infection such as tonsillitis, or occasionally they may be precipitated by the ingestion or administration of some substance to which the patient is subsequently found to be sensitive, e g tomatoes

The ætiology of this syndrome is considered to be an abnormal antigen antibody response

Pathology

There does not appear to be any characteristic lesion The appearances in advanced cases are the same as those found in acute or rapidly progressive glomerular nephritis There is pronounced cellular proliferation in the glomeruli both of the tufts and the capsules, focal collections of chronic inflammatory cells in the interstitial tissues, particularly around abnormal glomeruli, and glomerular fibrosis and tubular atrophy

Clinical Features

About 10–20 per cent of all cases of anaphylactoid purpura have hæmaturia and proteinuria, an acute nephritic syndrome may also be present. In the majority of these cases there is subsequently a rapid and complete recovery, while a few continue to excrete protein and red cells. In most of these proteinuria eventually disappears, but in the remainder it persists, chronic renal failure develops, and death occurs in one to five years. Recurrent attacks of macroscopical hæmaturia are a characteristic feature of this last group; they may also develop transient acute nephritic syndromes, and on occasion a nephrotic syndrome.

Approximately 10 per cent of those who have hæmaturia and proteinuria at the onset of an attack of anaphylactoid purpura die of chronic renal failure subsequently.

Treatment

It is doubtful if any treatment influences the course of the renal lesions; nevertheless, it is reasonable in the acute attack to treat any residual infection with antibiotics. In some instances it may be necessary to give prophylactic penicillin when there are recurrent relapses due to β-hæmolytic streptococcal infections.

Treatment of the advanced renal disturbances is unrewarding, though occasionally a patient may respond dramatically to ACTH or adrenal steroids; there are even some reports of complete cure. More often, however, adrenal steroids only produce a rapid rise in blood pressure, jugular venous pressure and blood urea, and treatment must be discontinued.

There have been claims, particularly by pædiatricians, that the administration of cytotoxic drugs is beneficial and life saving. Again these observations are uncontrolled.

LUNG PURPURA WITH NEPHRITIS

This is a devastating condition first described by Goodpasture and sometimes known as Goodpasture's syndrome. It is a rare condition which occurs particularly in young men between the ages of 18 and 26 years, and is most often seen during an influenzal pandemic. Following an upper respiratory or gastric type of influenzal illness there is a sudden onset of profuse hæmoptysis which lowers the hæmoglobin within a few days. Serial chest X-rays demonstrate the presence of fluctuating pulmonary shadows due to blood in the pulmonary alveoli. The presence of glomerular nephritis is usually detected a few days after the onset of the hæmoptysis. There is proteinuria, hæmaturia, and renal failure. Death usually occurs within a few months from renal failure; occasionally there is acute renal failure.

At post-mortem the kidneys show the structural changes of proliferative glomerular nephritis. The lungs contain collections of hæmosiderin in the alveoli and alveolar walls, with many histiocytes, both these changes are presumably consequent upon the hæmorrhage There is no other histological abnormality so that the cause of the hæmoptysis remains a mystery.

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21

ORTHOSTATIC PROTEINURIA

This benign condition is also called postural proteinuria. It consists of the excretion of protein in the urine only when the patient is in certain positions.

Ætiology

Proteinuria can be produced in 75 per cent of youths if they are placed in extreme lordosis; with increasing age the proportion gradually dwindles and, of men over 50, only 10 per cent will have proteinuria in this position.

It has been demonstrated that in the lordotic position the liver in these persons rotates forwards and downwards thus kinking the inferior vena cava. As a result there is a rise in the pressure within the inferior vena cava and renal veins, and protein appears in the urine.

If, however, the patient stands in the lordotic position but the liver is prevented from sliding forward by firm digital restraint under the right costal margin, the inferior vena caval pressure does not rise and there is no proteinuria. In bed, the lordosis of the upright position disappears and again there is no proteinuria, though it can be made to reappear by purposely assuming the lordotic position. Conversely, proteinuria will not appear in the upright posture if the patient remains bent forward.

Renal Function

Excluding the proteinuria renal function is normal.

Clinical Features

Orthostatic proteinuria occurs most frequently in children, adolescents and young adults. It has been reported in 12–40 per cent of children aged 10–16 years; and it is claimed that this proportion is greater if the urine is examined at frequent intervals. Orthostatic proteinuria occurs in about 5 per cent of young adults.

The presence of protein in the urine is usually detected during a routine examination on going to school or university, or on entering the services. Occasionally it is noted as an incidental finding during an illness which is unrelated to the kidney If many urine samples are tested it is found that protein is present throughout the day, except in *the first sample passed in the morning* The concentration of protein rarely exceeds ++ and is usually + or less, the daily excretion is seldom more than 2–3 g It is not unusual to find protein on some days and not on others Orthostatic proteinuria is of no importance, it does not influence the patient's health or the functional capacity of his kidneys *The majority of patients lose their proteinuria as they* become older though it may continue for 10–30 years

For routine purposes orthostatic proteinuria is distinguished from persistent proteinuria by asking the patient to empty his bladder just before going to bed, and to keep for examination the urine he passes *next morning immediately he gets up* This test can be combined with a 16- to 24-hour fluid deprivation test, when the ability to concentrate can be tested simultaneously

Differential Diagnosis

If proteinuria can be made to disappear with a change in posture *it is almost certain that there is no renal disease* Nevertheless it is also characteristic of the proteinuria of renal disease that it is greater when the patient is up and about, and diminishes upon lying down. On very rare occasions the proteinuria of renal disease may be altogether absent from the urine formed during the night, when it is then *indistinguishable from benign orthostatic proteinuria* These confusing cases usually declare themselves eventually, sometimes they can be differentiated earlier by an examination of the urinary deposit Orthostatic proteinuria should not be dismissed too lightly when it occurs in a patient over 30 years old

Treatment

No treatment is necessary

Proteinuria from Non-gonococcal Urethritis

Superficially, this appears to be a variant of orthostatic proteinuria, but in fact it has no direct relation to posture It is an important diagnostic trap The proteinuria is present in the *morning* and disappears during the course of the day The condition is most commonly seen in young men Urethal massage in the morning, before any urine has been excreted, and examination of the contents of the urethra establishes the diagnosis The two glass test is also a useful screening test

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22

RENAL INFECTIONS

Infections of the kidney can be divided into those due to the tubercle bacillus and those due to other organisms, only the latter are described below The outstanding features about pyelonephritis are the immense diagnostic difficulties, the lack of precise knowledge of the natural history of the condition and how it should be treated

INTERSTITIAL NEPHRITIS, RENAL INFECTIONS AND PHENACETIN NEPHROPATHY

Interstitial nephritis means inflammation of the interstitial spaces It is a structural abnormality which accompanies most renal diseases Unfortunately, the words involved in describing this disturbance, and the disturbance itself have been the cause of much confusion It is obvious that inflammation of the interstitial spaces must be due to some cause The semantic tradition which lingers on however, reserves the term interstitial nephritis mainly for those kidneys in which the cause of the inflammation is not known For instance, though the immunological diseases of the kidney are usually associated with inflammation of the interstitial spaces the characteristic changes in the glomeruli permit the overall changes to be defined as those due most probably to an immunological disturbance The interstitial changes are then either not mentioned specifically or referred to as an accompanying " inflammation of the interstitial spaces " In the same way the term interstitial nephritis is not used if an inflammation of the interstitial spaces is found in association with widespread deposits of calcium or collections of urate crystals, when the appearances are described as those of nephrocalcinosis and " gouty " nephropathy respectively Additional causes of inflammation of the interstitial spaces include bacterial and spirochætal infections, partial occlusions of the renal vasculature with or without hypertension, prolonged phenacetin administration, radiation nephritis, oxalosis, potassium deficiency, back pressure from obstruction to urine flow and lead poisoning Many of these, particularly if only a biopsy sample is available often show changes which are simply those of inflammation of the interstitial spaces and they cannot be distinguished one from another histologically.

That inflammation of the interstitial spaces must be due to some underlying cause, even when it cannot be discerned, preys heavily upon those who examine the structural appearances of the kidneys. They are inevitably tempted to ascribe causes when none are evident histologically. Their choice is then influenced by the clinical history, the blood pressure, the biochemical findings, the urine culture etc. Instead of reporting simply that the histological appearances are those of inflammation of the interstitial spaces of unknown cause, the histological changes are said to be due to ischæmia, infection, gout etc. This has inevitably given rise to the false impression that the various causes of interstitial inflammation *can* easily be differentiated histologically from each other, and that interstitial nephritis, i.e. inflammation of the interstitial space of unknown cause, is a most unusual condition. This self deception has been particularly prominent in English speaking countries where many authorities simply equate " interstitial nephritis " i.e. inflammation of the interstitial spaces of unknown cause, with pyelonephritis, i.e. inflammation of the interstitial spaces due to infection. This manœuvre neatly avoids the term interstitial nephritis and its connotation that the histologist can sometimes be baffled. It has been responsible for the ludicrous disparity between the various estimates of the incidence of renal infection in kidneys examined at autopsy (from 10 to 80 per cent!).

The following section is concerned with renal infection, and the excess ingestion of phenacetin, two causes of inflammation of the interstitial spaces which are often particularly difficult to distinguish histologically from other conditions which produce inflammatory changes in the interstitium.

ACUTE PYELONEPHRITIS

Including Acute Pyelitis and Acute Necrotising Papillitis

Ætiology

A wide variety of organisms may cause pyelonephritis; those found most frequently are *Escherichia coli, Klebsiella pneumoniæ, Pseudomonas pyocyaneus, Staphylococcus aureus, Proteus vulgaris* and *Streptococcus fæcalis.*

The majority of infections are associated with obstruction or deformation of the urinary tract; these cause a rise in pressure, and possibly a slowing in the rate of urine flow in those parts which lie proximal to the obstruction. About a third of infections, however, occur in kidneys with normal urinary tracts, nearly always in women. A few infections occur during a widespread and easily recognised dissemination of organisms from a primary focus, such as malignant endocarditis, osteomyelitis, empyema, etc ; the renal lesion thus caused is sometimes known as a "pyæmic kidney" but, as it is indistinguishable from severe acute pyelonephritis from other causes, it is included here. One of the commonest causes for such a bacteræmia is the introduction of a catheter, or cystoscope into a bladder containing infected urine

Lesions which obstruct the urinary tract include certain abnormalities of the renal parenchyma which deform the calyces, such as hypoplasia, polycystic kidneys, and scarring from previous infections (including tuberculosis) Other causes are congenital abnormalities of pelvis, ureter and urethra, aberrant renal arteries, renal and ureteric calculi, pregnancy, "neurogenic bladders", pelvic tumours, prostatic enlargement and urethral strictures Calculi and pregnancy are the two most frequent causes

Infections frequently complicate other parenchymal renal diseases, for instance, acute pyelonephritis may develop in a patient known to be suffering from renal polyarteritis nodosa In this connection it is interesting to note that animal experiments have shown that the intravenous administration of large numbers of Gram negative organisms only causes acute pyelonephritis if the ureters are temporarily occluded or the kidneys are already scarred from previous infections It has also been shown in animals that an increased susceptibility to infection can be produced by a period of potassium deficiency or hypertension The relation to hypertension is of immense significance.

The infecting organism may be conveyed to the kidney in (1) the blood stream, (2) the urine, from the bladder up to the lumen of the ureters, or (3) the lymphatics alongside the ureters Observations in human infection suggest that the organisms nearly always travel up the ureters Acute upper urinary infections in previously normal kidneys occur predominantly in women whose urine has contained large numbers of organisms for considerable periods before the onset of symptoms There is no doubt, however, that a transient bacteræmia can also cause pyelonephritis Occasionally (e g after routine catheterisation) the two mechanisms occur together, the bladder urine is first infected by the catheter, the organisms then multiply in the bladder and after an interval there is a simultaneous bacteræmia and acute pyelonephritis In animal experiments organisms have been introduced into the bladder after tying one ureter It has been found that the kidney with a patent ureter becomes infected while the other kidney remains intact, unless there is an associated bacteræmia The lesions in both human and animal infections are often most pronounced in the medulla In animals it has been shown that the medulla's ability to restrain bacterial growth is relatively poor This is due to the hypertonicity of the medulla which inhibits (i) the natural bactericidal activity of plasma, (ii) the mobilisation of white cells towards an injured area, and (iii) the phagocytic capacity of the white cells.

In a large proportion of cases the bacteria having ascended the ureter and invaded the highly vascular parenchyma, then spill into the blood and cause a septicæmia. In many more instances the bacterial invasion of the renal parenchyma is associated only with a rise in serum antibody titre to the infecting organism. This response is useful diagnostically particularly on those occasions when it is difficult to decide whether the organisms found in the urine have or have not recently invaded the renal parenchyma.

*Linnæan and other Names of some of the Organisms which cause Urinary Infections**

LINNÆAN NAME	OTHER NAMES	COMMENT
Escherichia coli	B. coli	The most frequent cause of acute urinary infections.
Staphylococcus aureus	Staph. pyogenes	Second most frequent cause of acute urinary infections.
Klebsiella pneumoniæ	Friedlander's bacillus Ærobacter ærogenes	Usually in mixed infections and when there are structural deformities of the urinary tract. Frequently after antibiotic therapy and indwelling catheter.
Pseudomonas pyocyanea	B. pyocyaneus Ps. æruginosa	
Proteus vulgaris	B. proteus	
Streptococcus fæcalis	Enterococci	Often follows catheterisation in women.
Hæmophilus influenzæ	B. influenzæ Pfeiffer's bacillus	Rarely found.

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* Hare, R. (1956). An Outline of Bacteriology and Immunity. Longmans, Green & Co., London.

Examination of the Urine for Evidence of Infection and Inflammation

The urine is cultured (see below) and examined microscopically for the presence of excess numbers of white cells. It is important to realise that a positive culture is evidence of infection, but not of inflammation, whereas an increased number of white cells is evidence of inflammation but not of infective inflammation. The two investigations are therefore complementary.

Urine Culture. It is no longer justifiable to catheterise the bladder to obtain urine for culture. Without a catheter however, some contamination of the urine by organisms which reside in the urethra or the vulva must often occur. It is imperative therefore that urine cultures should be quantitated for it is then possible to distinguish whether the organisms found in the urine are likely to be contaminants or whether they were present and multiplying in the bladder before micturition *If the urine is carefully collected (see below) and either cultured* immediately or kept cold until it is cultured, then a bacterial count greater than 100,000/ml has an 85 per cent probability of being due to true infection of the urine, a count of less than 10 000/ml is due to contamination Two consecutive cultures with counts greater than 100,000/ml. increase the probability that there is an infection to 99 per cent In a well run establishment counts between 10 000/ml and 100,000/ml should occur in less than 10 per cent of all urine cultures

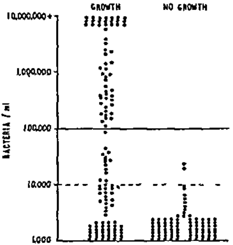

FIG 22 1 Routine urine culture report of growth and no growth compared with the number or organisms found on quantitative culture. Each dot represents one urine The interrupted horizontal line at 10 000 *organisms/ml and the continuous horizontal line at 100 000/ml* The block of dots at the bottom of the Fig represent counts of from less than 100/ml. to 2 000/ml and at the top of the Fig the block indicates counts greater than 10 000 000/ml (Bradley and Little 1963 *Brit med J*)

If they occur more frequently the urine is not being collected with *sufficient care When the count is between 10 000/ml and 100 000/ml* it should be repeated Pure cultures with only one type of organism support the probability that the organisms are multiplying in the bladder but only if the count is greater than 100,000/ml Pure cultures with counts below 10,000/ml have no significance These *interpretations of the significance of quantitative bacterial cultures do not* hold if the patient is on antibiotics The uselessness of culturing the urine in a non-quantitative manner is well illustrated in Fig 22 1 where a non-quantitative and a quantitative technique are compared It can be seen that a report of growth' from a non-quantitative culture gives no indication whether the urine is infected or contaminated.

Urine is collected from a woman after swabbing the perineum with benzalkonium chloride 1/1,000. The labia are then held open and the patient is asked to micturate. The whole volume of urine is collected, the first 10–50 ml. into one container and the remainder into a wide-mouthed autoclaved honey jar. Urine is obtained from a man in a similar way, after cleaning the urethral meatus with benzalkonium chloride 1/1,000. The urine in the autoclaved jar is cultured. If it is impossible to obtain a satisfactory sample of urine in this way either because of the patient's inability to co-operate or because it is difficult to prevent gross contamination, then it is permissible to pass a catheter into the bladder via the urethra. When a urine sample has been obtained in this way, 20 ml. of a 1 per cent solution of neomycin is injected into the bladder and left in situ just before withdrawing the catheter. In such patients suprapubic aspiration of urine from a full bladder is a useful alternative. This technique is also of use in distinguishing between contamination and infection when mid-stream urine samples from a patient repeatedly give bacterial counts between 10,000/ml. and 100,000/ml.

There are a variety of ways to perform quantitative cultures. For routine purposes it is only necessary to distinguish whether the count is greater than 100,000/ml. or less than 10,000/ml. Culturing the urine not only establishes whether or not the urine is infected but by typing the organisms it is often possible to judge whether the infection is due to a relapse of a previous inadequately treated infection or due to a reinfection. It also permits the sensitivity of the organism to various antibiotics to be established.

Examination of the Urine for Inflammation. The presence of an area of inflammation contiguous with the renal tract may be made manifest by the release of leucocytes into the urine. The methods used to determine the white cell content of the urine accurately are described on p. 33. It is necessary to mention that some reactionary routine laboratories refuse to culture a urine unless it contains more than a normal number of white cells. Conversely some clinicians are apt to ignore a positive urine culture if the number of white cells in the urine is not raised. Both practices are to be deplored. It is now well established that the urine may be heavily infected without its content of white cells being raised, particularly in patients with chronic pyelonephritis and symptomless bacteruria. In addition it cannot be stressed too often that the presence of an excess number of white cells in the urine is only evidence of inflammation. It does not follow automatically that this inflammation is due to infection with pyogenic organisms "Sterile" pyuria classically occurs in renal tuberculosis when it is strictly innaccurate to say that the urine is sterile *It also occurs in many other conditions* including acute glomerular nephritis, renal stones, and phenacetin nephropathy Of course it can also occur following an active renal infection with pyogenic organisms, for instance during recovery from an attack of acute pyelonephritis treated with antibiotics

Sometimes the presence of an active inflammatory focus in the renal tract is *not* accompanied by an excess number of white cells in

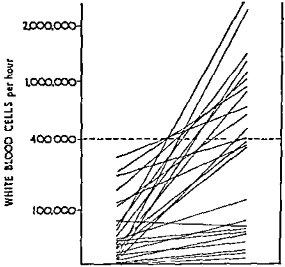

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FIG 22 2 White cell excretion rate before and after the administration of 40 mg prednisolone phosphate intravenously to 25 patients with radiological evidence of chronic pyelonephritis but in whom the urine was uninfected and the white cell content of the urine was normal In about *half of the patients there was a brisk rise in white cell excretion to a rate* above 400 000/hr indicating that though these patients urine was normal before the prednisolone injection an active focus of inflammation was still present adjoining the lumen of the renal tract (Little 1965 *J clin Path*)

the urine If, nevertheless, it is suspected that such a focus exists, its *presence may be revealed by giving the patient 40 mg of prednisolone phosphate intravenously, when there may be a prompt increase in* the number of white cells in the urine This test is particularly useful in investigating patients who have been given antibiotics for a supposed attack of acute pyelonephritis before the urine has been examined Later when the patient feels better and the urine is sterile, and contains a normal number of white cells the diagnosis of a recent urinary infection may be difficult to uphold The prednisolone test is also useful in patients with chronic renal infections who appear to be in an inactive stage (Fig 22 2) It is not known how prednisolone produces this effect. If the white cell excretion rate is raised without giving prednisolone there is clearly little point in doing a prednisolone test.

Pathology

The appearances of the kidneys depend largely on whether any underlying renal deformity was present before the onset of the acute infection. The following descriptions only refer to changes produced by infection. They are divided into three groups depending on their severity: (1) Acute pyelitis; (2) acute pyelonephritis; and (3) acute necrotising papillitis.

Acute Pyelitis. This is the term which pathologists give to an acute inflammation confined to the lining membrane of the renal pelvis, that is an infection which does not involve the renal parenchyma. At post-mortem such a limited distribution is found extremely rarely; it does not follow that it is equally infrequent in life. It is usually bilateral.

Acute Pyelonephritis. This is nearly always bilateral. Macroscopically the kidneys are usually enlarged and occasionally small abscesses show through the capsule. The surface may be discoloured by areas of pallor and congestion. On section, greyish wedge-shaped areas can be seen extending upwards from the pyramids into the cortex; there are also yellow streaks radiating from the medulla. The pelvis is red and covered with pus.

The pelvis microscopically is covered with an inflammatory exudate which penetrates within the pelvic wall; sometimes there are also areas of superficial necrosis. The renal parenchymatous lesions are more numerous in the pyramids and medulla. The tubules contain and are surrounded by leucocytes, though occasionally these are confined to the interstitial tissues. There are similar collections of neutrophils in the interstitial tissues of the cortex, in addition, some glomeruli become selectively invested by a thick concentration of acute inflammatory cells. In a few, the capsule is breached and leucocytes can be seen invading the glomerular space. In some sites an inflammatory destruction of tubules may cause a crowding together of glomeruli which are then separated only by granulation tissue. A varying number of small abscesses may be disseminated throughout the renal parenchyma and, before the use of antibiotics, bacteria were also found in large numbers.

The vascular lesions are of particular importance, and in this connection it should be recalled that the renal pelvis extends as far upwards as the cortico-medullary junction (p. 5). It is not surprising, therefore, to find that sometimes the acute inflammatory process involves some of the larger arteries and veins. Dense infiltrations with leucocytes may be localised in the arterial wall, leading to destruction of the muscle and elastic tissues, occasionally this process leads to occlusion of the lumen by a thrombus, and complete infarction of wedge shaped areas of cortex Other large arteries may show moderate degrees of narrowing of the arterial lumen by endarteritis In the areas of acute inflammation thrombosis of arterioles is relatively frequent

Acute Necrotising Papillitis This consists of an acute pyelonephritis of such severity that there is a focal suppurative necrosis of one or more renal pyramids The process begins at the apices of the pyramids and extends upwards into the medulla, but does not involve the cortex. Microscopically there is a dense purulent exudate throughout the affected area which is sharply demarcated from the viable parenchyma

Clinical Features

The signs and symptoms are those of an acute upper urinary infection There is a sudden onset of fever, pallor and rigors, with pain and tenderness in the loins and the flanks, and the presence in the urine of large numbers of white cells and bacteria, proteinuria is rarely greater than a " trace " to + Frequently there is much nausea and vomiting, and with severe attacks there may be gross macroscopical hæmaturia. If there is also inflammation of the lower urinary tract there will be frequency of micturition, dysuria and lower abdominal pain and tenderness The clinical features give no clue to the identity of the infecting organism

As it is clinically difficult, particularly at the onset, to differentiate between acute pyelitis and pyelonephritis, and as a substantial number of clinically mild cases may show inflammatory lesions in the cortex (renal biopsy), it is best to consider that all upper urinary infections involve the renal parenchyma, i e that all such infections are due to acute pyelonephritis

The extent of the parenchymatous involvement depends mainly on the presence of urinary tract obstruction, the greater the obstruction the more extensive the infection Such obstructions are often found in patients of either sex who have recurrent infection, they underlie most upper urinary infections that occur in men, whereas women mostly have recurrent infections without any abnormality of the urinary tract.

Renal function in upper urinary infections may be unaffected, or it may be so severely impaired that the patient dies from acute renal failure Characteristically renal function returns to its previous level as the infection subsides The magnitude of this transient impairment is probably of some value in assessing the amount of parenchyma that has been invaded in the acute inflammatory process

Proper appraisal may be difficult if some degree of renal failure preceded the infection; at such times renal function should be re-examined a few weeks after the infection has been controlled.

Acute Necrotising Papillitis. This occurs most often in elderly diabetics, most of whom have suffered from previous upper urinary infections. In addition to the usual features of a severe acute upper urinary infection, hæmaturia occurs frequently and, if the lesion is bilateral, there is a sudden reduction in urine flow, and the onset of acute renal failure. Sometimes pieces of necrosed papillæ appear in the urine. If the patient recovers, the loss of part of one or more papillæ may be defined in an I.V.P. or retrograde pyelogram.

Recently there have been reports of patients on continuous sulphonamide therapy for chronic urinary infection who have developed renal colic or ureteric obstruction due to the necrosis of a papilla without any evidence of an associated acute infection. Necrosis of papillæ also occurs in phenacetin nephropathy (p. 300).

Relationship between Clinical and Structural Features. Renal biopsy studies have shown that in acute pyelonephritis there is a striking lack of correlation between the severity of the constitutional symptoms and impairment of renal function on the one hand, and histological appearances on the other. The main reason for this discrepancy is probably the focal nature of the disease.

The most important observation is that severe acute pyelonephritic lesions of the cortex, with inflammatory cell replacement of the tubules, can be obtained from patients who, clinically, have suffered only from a mild " pyelitis." In one series such lesions were found in one quarter of a group of patients with clinical signs and symptoms of an acute upper urinary infection. As autopsy findings have shown that pyelonephritic lesions in general are focal, and more advanced in the medulla, these findings suggest that nearly all patients with an upper urinary infection have destructive lesions of the cortex and medulla.

It is interesting to note that it is unusual for these acute destructive lesions to be associated with any recognisable change in the intravenous pyelogram at the time of the infection. The abnormalities which may occur include a diminished density of the radio-opaque medium on the most affected side, localised renal swelling, and compression and elongation of one calyx. The difference in density is not a helpful finding, while the other two abnormalities are rare.

Sequelæ of Acute Pyelonephritis. If the pyelogram is repeated a few months to a few years later, changes will be evident, the nature of which will depend on the patient's age. In children, serial pyelograms often reveal the development of gross cortical scarring with clubbing or distortion of one or more calyces. In adults, cortical scarring and clubbing and distortion of calyces do not develop, but the kidneys show a reduction in their lengths of 0 6 to 6 0 cm, which confirms the renal biopsy findings that clinical acute pyelonephritis in adults is usually associated with some destruction of the parenchyma. The radiological appearances of cortical scarring with distortion and clubbing of calyces are referred to as those of chronic pyelonephritis (p 292) They may be found for the first time in children or adults who have never suffered from an overt attack of acute pyelonephritis It must be stressed that as these changes do not develop after childhood, they are always evidence of childhood renal infection

It is not clear why destruction of the renal parenchyma in children should be associated with such marked overall structural changes while in adults the overall effect is radiologically so much less pronounced There is some evidence that acute pyelonephritis in childhood is a more destructive disease which may account for part of the difference In addition the distortion produced by those parts which have been destroyed may be accentuated by the continued growth of those parts which have escaped destruction

Prognosis

An acute infection of the renal parenchyma may cause death, either if it is sufficiently extensive, or if it is superimposed upon pre-existing chronic renal disease (e g chronic pyelonephritis)

Once the acute infection has been controlled, the risk of further attacks and the development of chronic pyelonephritis depends a great deal on whether or not there is permanent deformity of the renal tract or ureteric reflux (p 298) Usually such deformities precede infections, but the changes produced in the renal parenchyma and pelvis by sufficiently severe or recurrent infections may themselves perpetuate the tendency to infection and the development of chronic pyelonephritis

It is essential to remember that a patient suffering from advanced renal failure secondary to an acute renal infection may rapidly recover once the infection is controlled, it is unwise, therefore, to give a prognosis during the acute phase of the infection

Differential Diagnosis

Fever, rigors, tenderness and pain in one or both loins suggest, and the finding of pus and organisms in the urine confirm, the diagnosis Occasionally when local symptoms and signs are absent, the diagnosis only becomes apparent after a routine examination and culture of the urine The finding of a high serum antibody titre to the bacteria present in the urine is presumptive evidence that the organisms have invaded the parenchyma. *An acute urinary infection should always be* *kept in mind when the patient is known to suffer from some other chronic parenchymal renal disease.*

It has been shown, by culturing organisms from renal biopsy material, that parenchymatous renal infections may occur without organisms appearing in the urine. The frequency of this condition is not known; the cases described had pyrexia of unknown origin, proteinuria and some mild impairment of renal function.

Investigation of Underlying Urinary Tract Abnormality. The structural integrity of the kidneys and of the urinary tract should be investigated following (1) any upper urinary infection occurring in a boy or a man, (2) a second infection in a woman, (3) a first infection in a woman if it is accompanied by renal colic, hæmaturia, impaired renal function, or followed by persistent proteinuria or large numbers of white cells in the urine. Intravenous and retrograde pyelograms are usually sufficient, though occasionally arteriograms and even laparotomy may be needed.

Treatment

Prophylactic. If organisms are introduced into a normal bladder which can empty completely the bacteria are evacuated, persistent bacteruria does not develop and acute pyelonephritis is most unlikely to occur. On the other hand, if bacteria gain access to the bladder of any individual who suffers from some deformity of the renal tract including lesions which cause some residual urine to be present after voiding, the chances of developing persistent bacteruria and an overt symptomatic urinary infection thereafter are very great. Bacteria are most likely to gain access to the bladder during catheterisation and urological investigations. The incidence of bacteruria following these manœuvres can be reduced by introduction into the bladder of an antiseptic or antibiotic at the end of the procedure. It is also wise to culture the urine of patients with known abnormalities of the renal tract from time to time. If the urine is infected it should be sterilised by a short course of antibiotic, routine cultures being continued thereafter. Another way in which organisms commonly enter a woman's bladder for the first time is at the beginning of active sexual life. At this time acute pyelonephritis occurs relatively frequently even in those who have a normal renal tract. There is much to be said for giving all virgins 100 mg. of nitrofurantoin to take at night for the first two or three weeks after they cease to be virgins.

Acute pyelonephritis occurs predominantly in those individuals who have asymptomatic bacteruria. In schoolgirls the incidence of asymptomatic bacteruria is about 1 per cent. After puberty it rises to about 6 per cent where it remains until the age of 60 to 70, when it rises again to 20–30 per cent in the elderly The rise after puberty is due to sexual activity, for the incidence among nuns is the same as in schoolgirls before puberty The incidence of acute pyelonephritis in women with asymptomatic bacteriuria varies from group to group For instance, it is highest in pregnant women in whom 25–30 per cent of those with asymptomatic bacteriuria develop acute pyelonephritis It is much less in women who are not pregnant (but the actual incidence is not known) There is no doubt that the detection of those pregnant women who have asymptomatic bacteriuria and the sterilising of their urine with antibiotics can greatly reduce the incidence of acute pyelonephritis in pregnancy (p 328) There is a growing feeling that a similar search for and treatment of asymptomatic bacteriuria should be undertaken in infants and children

Control of the Acute Infection Patients used to recover from acute upper urinary infections before the arrival of antibiotics It is probably true, therefore, that many infections would recover if treatment were limited to the administration of large quantities of water and sodium citrate In practice it is best to give an antibiotic in all upper urinary infections, for if the inflammatory process has penetrated into the renal parenchyma it is reasonable to suppose that quick control of the infection will lessen the residual damage

Sulphonamides are usually administered without first identifying the organism responsible for the infection The repeated success of this blind manœuvre ensures its continuity, but there is no doubt that it is more satisfactory to culture the urine and determine the sensitivity of the organism When there are recurrent infections it is imperative that this be done Antibiotics are excreted in the urine at varying rates, but in all instances their urinary concentration is greater than their simultaneous concentration in body fluids Contrary to original expectations it is only necessary to give sufficient antibiotics to obtain an effective urinary antibacterial level The administration of antibiotics should be continued for at least three weeks, and certainly *for some days after all trace of tenderness in the loins has disappeared*

When there has been evidence of extensive parenchymal invasion, that is if renal function has been depressed by the infection, it is advisable to continue treatment for two to three months

The choice of antibiotic is determined by the sensitivity of the infecting organism, but if the diagnosis is clear cut it is unnecessary to wait 24 hours for the result of urine culture, treatment is started with either sulphadimidine (3 g followed by 1 g 6-hourly) or tetracycline (0 25 g 6-hourly) immediately after some urine has been obtained for culture In this way no time will have been lost whatever

ANTIBIOTICS USED TO TREAT URINARY INFECTIONS

Antibiotic	*Dose*	*Methods of Administration*	*Comment*
Sulphadimidine (Sulphamezathine)	3 g. loading dose 1 g. 6-hourly	Oral administration—intramuscular and intravenous preparations available.	Particularly useful in acute infections. Emphasise need to drink much fluid.
Penicillin G	800,000 units 6-hourly.	Oral or intramuscular.	Wide range at this dosage. Toxicity minimal except for sensitivity. Useful in renal failure.
Nitrofurantoin (Furadantin)	100 mg. 8-hourly. 50–100 mg. 8-hourly for maintenance.	Oral—after meals preferably—intravenous preparations available.	Wide spectrum—particularly useful against *B. Proteus* infections. Occasionally Hæmolytic jaundice, peripheral neuropathy in patients with renal failure.
Ampicillin (Penbritin)	500 mg. 8-hourly.	Oral and intramuscular.	Wide spectrum—no toxicity except occasional sensitivity in patients with renal failure.
Tetracycline	0·25 g. 6-hourly.	Oral, intramuscular and intravenous.	Wide spectrum—very useful antibiotic. Excellent for *Proteus morgani*. Do not use in renal failure—causes increase in blood urea.
Methenamine mandelate (Mandelamine)	1 to 2 g. 8-hourly.	Oral only. Urine must be acid. Give ammon. chlor or methionine or ascorbic acid.	The least toxic urinary antiseptic—useful for *B. coli*, *Staph. aureus* and *Strep. fæcalis* infections with methionine, useful for *B. proteus*.
Naladixic acid (Negram)	1 g. 6-hourly.	Oral.	Gram -ve, *B. proteus* particularly. Can be used in advanced renal failure.
Cephaloridine (Ceporin)	1 g. b.d.	Intramuscular and intravenous.	Wide spectrum—no toxicity. The best antibiotic for use in advanced renal failure.
Streptomycin	1 g. b.d. for 3 days or 1 g. a day for 10 days.	Intramuscular. Best effect if urine is alkaline. Give sodium citrate 2 g. 6-hourly.	Useful against organisms resistent to other antibiotics, particularly recurrent infections. Best used as a short, heavy attack on the infection before beginning continuous therapy with some other drug. Adjust dose to G.F.R.
Kanamycin	1 g. per day.	Intramuscular and intravenous.	Same indications and complications as streptomycin.
Colistin methane sulphonate (Colomycin)	120 mg. 8-hourly.	Intramuscular.	Particularly for *Pseudomonas Pyocyaneus*. Ototoxic complications.
Gentamycin	1 mg./kg. per day in 3 divided doses.	Intravenous or intramuscular.	Particularly useful against *Pseudomonas pyocyaneus* resistent to Colomycin. Ototoxicity marked.
Cycloserine	250 mg. alternate days.	Oral.	Wide range but acute mental disturbances frequently occur.

the result of culture Other antibiotics are listed in the Table opposite It is useful to remember that many antibiotics may themselves cause renal damage A few, such as sulphamerazine, and bacitracin do this so frequently that they should be avoided

During a course of treatment the urine should be cultured at least once to make certain that the antibiotic is effective When the course of antibiotic is finished the urine should be cultured approximately 2, 7, 14 *and 30 days later and then at monthly intervals* The treatment and prevention of further attacks is discussed below

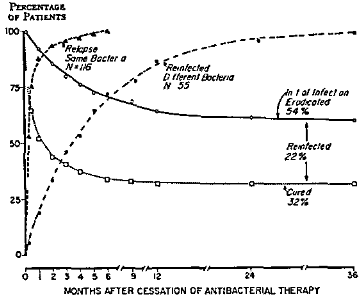

FIG 22 3 Rate of relapse and reinfection in 252 patients with urinary infections after treatment. The upper curve on the left demonstrates the recurrence of bacteruria with the original infecting strains It shows that nearly all *the relapses that occurred in the three years of follow up had occurred* in the first three months whereas the re-infections occurred at a slower pace and continued throughout the study (McCabe and Jackson 1965 *New Eng J Med*)

Precautions in Patients with Renal Failure. Most drugs are excreted in large amounts in the urine so that their plasma and urine concentrations are closely related to the state of renal function When renal function is impaired the plasma level of such drugs may rise to *toxic levels (e g streptomycin and nitrofurantoin) while conversely* their concentration in the urine may fall to such low levels that the concentration is insufficient to sterilise the urine even if the organism is sensitive Cephaloridine, ampicillin and nalidixic acid are the safest *drugs to use in the presence of severe renal impairment*

Tetracycline should not be given to patients with renal failure for its effect on protein metabolism causes a brisk rise in blood urea and other nitrogenous waste products.

Prevention of Further Attacks. Relapses of infection with or without symptoms, i.e. recurrences of bacteruria with the same original infecting organism will all occur within three months of ceasing treatment whereas reinfections, i.e. the acquisition of new infections with a different strain will occur mainly in the first year, and continue more slowly thereafter (Fig. 22.3). If relapses and reinfections are not differentiated there is an overall recurrence of bacteruria within six months in 50 per cent of patients who have had an attack of acute pyelonephritis; and at the end of 18 months 80 per cent will have had a recurrence of bacteruria. Symptomatic attacks of acute pyelonephritis recur in a proportion of those who redevelop bacteruria.

The prevention of recurrence is often a surgical procedure, with the repair or removal of a structural deformity. Otherwise the prevention of further attacks depends on keeping the urine sterile. This can be done in one of three ways. The first consists of giving a short course of an appropriate antibiotic in normal doses, each time the urine is found to be infected *or* symptoms recur. In order that treatment should be prompt the patient keeps a supply of one of the wide spectrum oral antibiotics at home. Urine cultures are performed at regular intervals. Alternatively urinary sterility can be maintained by giving long courses of a simple urinary antibiotic in small doses. The antibiotic is given once in the 24 hours and is best taken at night on retiring. During the night the concentration of the urine is at its highest so that the concentration of the antibiotic is also at its highest, this urine remains in the bladder for some considerable time, and the bladder at this time is therefore in an advantageous position to repel any bacterial invasion introduced during sexual intercourse. Sulphadimidine 0·5 g., sulphamethizole 200 mg., nitrofurantoin 100 mg. or nalidixic acid 1 g. have each been found useful, particularly nitrofurantoin. Side effects from such small doses are unusual.

If none of these methods prevents frequent reinfections of the urine but the patient does not develop overt clinical symptoms it is probably best to continue whichever treatment is being given and to watch and wait. If, on the other hand, frequent reinfections of the urine are associated with frequent attacks of overt and symptomatic attacks of urinary infection it may be necessary to give larger amounts of antibiotics and to use a different antibiotic each week to try and prevent the organisms becoming resistant. Nitrofurantoin 100–200 mg. per day, sulphamethizole 100 mg. four times a day, tetracycline 250 mg. three times a day, nalidixic acid 2 g. per day, benzylpenicillin 500 mg.

four times daily and ampicillin 250 mg four times a day have been used in this way Other drugs such as streptomycin, kanamycin, colistin and cephaloridine may be used in standard doses if infections occur in spite of this treatment

CHRONIC PYELONEPHRITIS

Pathology

The kidneys are small, coarsely and irregularly misshapen by scars and areas of hyperplasia of widely differing dimensions The extent of the damage is often more pronounced on one side than on the other and is sometimes entirely unilateral The cut surfaces show scars extending from the pelvis to the capsule

The microscopical appearances consist of patches of intense infiltration with lymphocytes and plasma cells, these areas are distributed in a haphazard manner, but concentrated more in the medulla than in the cortex The tubules in these sites are either small and atrophic,

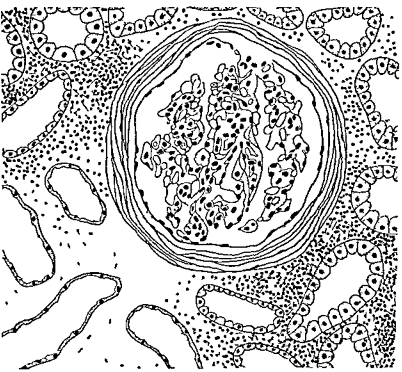

FIG 22 4 Chronic pyelonephritis Schema illustrating the following changes a fibrous scar atrophic tubules chronic inflammatory cells and one glomerulus which is surrounded by a thick halo of fibrous tissue but whose tuft is intact The relatively normal tubules are separated by much intertubular material or dilated with flattened epithelium and contain collections of a homogeneous eosin staining material (" thyroid areas "). The glomeruli resist the inflammatory invasion better than the tubules; some may appear almost unchanged while others have normal tufts, though they are surrounded by a thick collar of fibrous tissue (Fig. 22.4); the remainder, however, show varying degrees of change in the tufts, including fibrosis and atrophy.

Frequently the changes of acute pyelonephritis are found interspersed and superimposed upon those of chronic pyelonephritis.

The scarring is principally due to wedge-shaped areas of inflammation, but there may also be similar shaped areas of ischæmic infarction; often the two are histologically inseparable. The extent of the vascular changes is very variable, but in those patients who have suffered from severe hypertension, advanced changes are always seen, both in the larger arteries and in the arterioles. The arcuate, interlobar and interlobular arteries show gross thickening of focal areas of the external elastic lamina with fibrous replacement of varying amounts of the arterial walls, including the elastic and muscle coats; they may also show extensive fibrocellular proliferation of the intima. These changes produce extreme narrowing of the lumen, though complete occlusion is rare. The arterioles show the changes associated with either malignant or non-malignant hypertension. Whenever there are malignant hypertensive changes there are also widespread and severe changes in the larger arteries.

Discussion on the Development of Structural Changes

About 70 per cent of the incidence of chronic pyelonephritis, i.e. gross focal scarring with distortion of the calyces is due to some associated structural abnormality of the urinary tract. These abnormalities have been described in the section on acute pyelonephritis and are usually identified without great difficulty. The most important are those which have been present since birth. There remains a relatively large group of patients with gross focal scarring and distortion of calyces in whom no apparent abnormality of the renal tract can be demonstrated. In this group, as in the overwhelming majority of the other group, the cortical scarring and distortion of the calyces *only develop in childhood.* It follows that if the recognition of chronic pyelonephritis is considered to depend on the presence of radiologically evident focal scarring and calyceal distortion, chronic pyelonephritis does not *develop* in adults.

It does not follow that repeated or persistent infection of the kidneys beginning in adulthood cannot cause destruction of the kidneys and eventual death of the patient. It might do so without causing gross radiologically evident focal scarring and distortion of calyces Such a possibility is supported by the fact that if a patient with childhood chronic pyelonephritis, i e with gross scarring and calyceal distortion, survives into adulthood the radiological abnormalities will show little further change even though the patient may eventually die of chronic renal failure Presumably continuing destruction of the kidneys by infection in adulthood does not cause further areas of focal scarring sufficiently extensive to be apparent radiologically. The suggestion that infection of the kidneys in an adult *may* cause destruction without gross scarring and calyceal distortion is also supported by the finding that acute pyelonephritis in adults is often followed by a reduction in the size of the kidneys, but as has been mentioned above cortical scarring and distortion of calyces does not occur

If it is accepted that renal destruction by infection in adults can occur without the characteristic radiological appearances of chronic pyelonephritis ’ it is clear that the diagnosis of chronic renal infection in adults is going to be difficult Renal biopsies are only of limited help (p 275) while abnormalities in urine cultures and white cell excretion rates from bladder urine do not indicate the site responsible for the abnormality Often the diagnosis is just as difficult at autopsy for it is well established that even in patients with the classical focal scarring and distortion of calyces who have died of chronic renal failure the kidneys may contain no organisms In the *absence* of the characteristic macroscopic scarring and calyceal changes *and* organisms, the evidence on which a diagnosis of chronic renal infection can be made is limited to a subjective interpretation of the microscopical appearances

The absence of organisms at post mortem even in kidneys which have indubitably been the site of severe focal infection in the past, and in which the destruction has continued thereafter in a less focal way, is difficult to explain In animal experiments there is some suggestion that bacterial antigens may remain in the kidneys after the *death of the bacteria and cause a continuing inflammatory reaction* in the absence of live organisms There is also some evidence that though conventional methods of bacterial culture may fail to reveal bacteria, *other methods will reveal bacterial variants such as protoplasts* These are conventional organisms without their capsules In this state they can only exist in hypertonic media As the renal medulla is the only persistently hypertonic area in the body and as it is also particularly susceptible to infection (p 278) it is possible that some of the continuing destruction of the kidneys in patients with “ sterile ’ urine is due to infection with protoplasts

Antikidney antibodies cannot be found in chronic pyelonephritis either circulating or deposited in the kidney It does not appear there fore that the process of destruction is related to that involved in the immunological diseases of the kidney.

Clinical Features

In many respects the following description is concerned with the clinical features of all forms of chronic pyelonephritis. Nevertheless in stressing the difficulties of diagnosis it is concerned particularly with that group of patients in whom the disease is not associated with some abnormality of the urinary tract. This group consists mainly of children, and women below the age of 40.

Aside from those patients in whom the development of chronic pyelonephritis has been preceded by recurrences of acute pyelonephritis the first indication that the disease is present may be:

1. Proteinuria in a " symptomless " patient.
2. Hypertension and proteinuria in a " symptomless " patient.
3. Advanced renal failure in a previously " symptomless " patient.
4. A chronic intermittent illness with vague general symptoms and proteinuria.
5. A recurrent illness with vague general symptoms but some localised signs, including loin pain, dysuria, fever and proteinuria.

It is clear that often the diagnosis is not made before the onset of hypertension, renal failure or cardiac failure. This is due, in part, to the patient's being truly symptomless before the disease is well advanced, but also to the fact that even when there are symptoms both the patient and her attendant are apt to minimise their importance.

Frequency and dysuria occur in about half the cases but often they only last a few hours and disturb the patient very little. Intermittent pains in the loins afflict nearly three-quarters of all cases, but direct questioning may be needed to elicit their presence. Thirst and polyuria are rather more common than in other forms of renal failure, but it is not often that they are sufficiently pronounced to cause comment. Many patients will admit to intermittent spells of tiredness, headache and loss of appetite.

Characteristically, the urine is infected (i.e. there are more than 100,000 organisms/ml. of urine), and contains an excess number of white cells (i.e. more than 10/c.mm. or more than 400,000/hour). In addition proteinuria is usually present though it is seldom greater than 5 g./24 hours. The absence of these abnormalities does not exclude a diagnosis of chronic renal infection. Alternatively, when a diagnosis of chronic pyelonephritis has been made on radiological evidence, the absence of urinary abnormalities does not necessarily mean that the inflammatory process is quiescent An injection of prednisolone phosphate intravenously may provoke a sudden rise in white cell excretion (p 281) and demonstrate that a site active of inflammation does exist

It must be stressed that the finding of bacteria, white cells and protein in the urine is not sufficient evidence on which to base a diagnosis of chronic pyelonephritis During life the only accepted criterion, at the present time, is radiological evidence of focal *parenchymal scarring with calyceal distortion In those patients in* whom there is some clinical suspicion that the kidneys are the site of persistent infection and in whom there is bacteriuria and pyuria, and yet the radiological appearances are normal or equivocal, it is sometimes possible to clinch a diagnosis of renal infection by catheterising the *ureters It is then possible to do quantitative counts on the urine coming* from each kidney The technical procedures involved in avoiding contaminating the ureteric urine with bladder urine are not difficult but must be scrupulously carried out Otherwise, the results are meaningless If the ureteric urine is infected it seems reasonable to *suppose that the renal parenchyma is infected Whether or not such* cases are to be considered as having chronic pyelonephritis is a matter for semantic bickering

In keeping with the focal nature of the disease it is characteristic that there is often a marked difference in renal function between the *two kidneys This information can often be inferred from the inequality* in renal size but is most accurately obtained with ureteric catheters The most revealing parameters to study are the ability to concentrate the urine, the urinary sodium and creatinine concentration and the creatinine clearance The investigation is performed at the end of a period of fluid deprivation or after the injection of 5 units of vasopressin tannate in oil intramuscularly It is performed mainly when a unilateral nephrectomy is being contemplated particularly if there is hypertension The investigation allows an assessment to be made of the likelihood of the remaining kidney being able to sustain life and may also give some indication whether the hypertension is due to a superimposed renal ischæmia and therefore whether unilateral nephrectomy will reduce the blood pressure *In both pyelonephritis and ischæmia the ability* to concentrate and the creatinine clearance will be reduced In the predominently ischæmic kidney, however, the urinary sodium concentration will be lower and the creatinine concentration higher than on the opposite side whereas in the predominently pyelonephritic kidney *the urinary sodium concentration* will be the same or higher and the creatinine concentration lower than on the other side

In general, renal functional impairment follows the same pattern as that described in the section on chronic renal failure (p. 165), but there tend to be certain divergences, particularly in the early stages, which may be useful in establishing the diagnosis. For instance, tubular function is apt to deteriorate more rapidly than glomerular filtration rate. It is not unusual, therefore, to find an inability to concentrate the urine above S.G. 1·012, while the creatinine clearance is still approximately 50 ml./min., and the blood urea 40 mg. per 100 ml. For the same reason there may be an apparently exaggerated diminution in the ability to excrete hydrogen ions with a consequent fall in plasma *p*H and bicarbonate. When the glomerular filtration rate is only moderately impaired, however, and there is little or no accompanying rise in plasma phosphate concentration the fall in plasma bicarbonate is compensated for by a rise in chloride and there is a hyperchldoræmic acidosis. In some patients with prolonged severe active chronic pyelonephritis there may be a considerable increase in the plasma concentration of gamma globulins together with a high sedimentation rate. A finding such as this in a patient in whom the presence of chronic pyelonephritis is not known may cause some confusion. The renal impairment and abnormal electrophoretic pattern may suggest a diagnosis of myelomatosis. After treatment with antibiotics the erythrocyte sedimentation rate and the plasma protein pattern gradually return to normal.

Relationship Between Clinical and Structural Features

Histological evidence compatible with chronic pyelonephritis can be obtained with a renal biopsy before there are any changes in the I.V.P. There is no relationship between the severity of these structural changes and renal functional impairment or the severity of " pyuria," (i.e. visible pus in the urine). Pyuria usually occurs with renal calculi or some gross structural deformity of the urinary tract, and it is probable that these large quantities of white cells are coming from the pelvis or ureter. This is in keeping with the well-known clinical observation that some patients may excrete considerable amounts of pus each day for years without any marked deterioration of renal function.

Differential Diagnosis

In the absence of the characteristic radiological appearances it is extremely difficult to find out if the patient is suffering from a chronic renal infection. Some support will be obtained by being able to exclude other renal diseases which cause proteinuria and impairment of renal function. Clearly this is not easy. The main point of differentiation between pyelonephritis and nearly all other renal diseases is its focal nature and that it so often affects one kidney more than the other It is also useful to remember that chronic pyelonephritis is the most common cause of predominantly unilateral renal disease

When there are radiological changes suggestive of chronic pyelonephritis the two main problems of differentiation are back pressure atrophy and ischæmic scars Back pressure atrophy often follows a short period of ureteric obstruction, the radiological appearances remaining abnormal thereafter Back pressure atrophy is characterised by a generalised and uniform loss of renal substance which is equal throughout the kidney, this change is nearly always associated with a uniform loss of papillæ, and often with a dilatation of the renal pelvis and calyces Radiologically focal ischæmic scarring is differentiated from pyelonephritic scarring by the fact that ischæmia does not distort the calyces

Course and Prognosis

Occasionally the onset of the disease can be traced back to an acute upper urinary infection which occurred many years earlier, and which was followed thereafter by intermittent mild relapses. More often, the past is as indefinite as the future is uncertain

It is characteristic of the progress of chronic pyelonephritis that renal functional impairment may either remain unchanged for 10–20 years, or suddenly become so much greater (due to an acute infection) that the patient dies within a few days It is equally characteristic that, though an almost terminal state of renal failure may be provoked by an acute infection, an unexpected recovery may take place. For these reasons it is impossible to gauge the prognosis in an individual case until there is persistent and advanced renal failure, or malignant hypertension has developed About half the patients with chronic pyelonephritis have a normal blood pressure, but it is nevertheless the renal disease which most frequently gives rise to malignant hypertension Established hypertension is often aggravated by a clinically obvious flare up of infection

Unilateral Chronic Pyelonephritis and Hypertension

It is difficult to predict which patients will have a fall in blood pressure following a unilateral nephrectomy The combination of pyelonephritis and ischæmia makes the interpretation of individual renal functional studies difficult, for each produces opposing functional changes A few patients have had their blood pressure successfully lowered in spite of ureteric studies which suggested that the kidney which was removed was not ischæmic (p 116) Many of the successful operations have been in patients who had an acute and accelerated form of hypertension of short duration, including malignant hypertension. Operations on patients with unilateral renal disease and hypertension should not be performed until the functional integrity of the other kidney has been investigated. If one kidney is small the other should be large. If the supposedly normal side is not bigger than normal then it is itself diseased.

Some authorities consider that before deciding to do a nephrectomy a renal biopsy should be obtained from both kidneys (with an interval between the two biopsies), and that the likelihood of lowering the blood pressure will be greater in those in whom the kidney to be removed shows no arteriolar changes, whereas they are present on the other side. This demonstrates that there is some arterial occlusion between the main renal artery and the arterioles.

Chronic Pyelonephritis and Vesico-ureteric Reflux

In many patients with the characteristic I.V.P. appearances of chronic pyelonephritis vesico-ureteric reflux can be demonstrated. This consists in showing that a radio-opaque liquid placed into the bladder, and then spontaneously evacuated, ascends up either one or both ureters during micturition. Occasionally the patient may have complained of intermittent pain in the loin during micturition.

There is no doubt that unless infection is controlled, reflux hastens the rate at which the infection destroys the kidney. There are now several reports, however, in which it has been shown that reflux, particularly in children, has disappeared following the prolonged administration of antibiotics. Surgical correction of reflux can be a relatively simple procedure if the reflux is due only to bladder neck obstruction. But when the reflux has to be treated by operations on the ureter the results are unpredictable and often unsatisfactory. The success of these operations seem to depend, more than most, on the skill and the experience of the surgeon.

Chronic Urinary Infection and Renal Stones

There is no doubt that the presence of renal stones often causes urinary infections, but there is also some evidence that infection itself may cause stone formation. The main factor which is probably responsible is the urea splitting properties of some organisms such as *B. proteus*; ammonia is formed and the urine becomes, and remains, highly alkaline, which leads to the precipitation of calcium phosphate. This mechanism is exacerbated if there is increased calcium excretion due either to excessive calcium intake (milk) or prolonged rest in bed (e.g. poliomyelitis).

Treatment

If the disease has extensively involved one kidney and the other is sound it is usually wise to remove the diseased kidney, for, if the blood pressure is not raised preoperatively, the operation will prevent its rising, and, if it is already raised, the operation may cause it to return towards normal Nevertheless, if the kidney is not causing any symptoms, the urine is uninfected and the blood pressure is normal, it may occasionally be justifiable to do nothing except keep the patient under observation

In bilateral disease any surgically treatable cause of urinary tract deformity, such as renal stone and ureteric strictures, should be attended to, but it is doubtful, once chronic pyelonephritis is established, whether surgical procedures will completely halt its progress Postoperatively these patients should therefore be treated in the same way as those in whom no primary deformity of the urinary tract is discoverable, or in whom such a deformity is inoperable

Once a diagnosis of chronic pyelonephritis has been made, the aim of treatment is to try and prevent the infection from smouldering or suddenly flaring up The ways in which further infections may be prevented are outlined on p 290 Continuous and prolonged attention should be maintained by the patient and her doctor to detect any minor change in general condition, and the urine should be examined frequently If the patient experiences similar symptoms to those she has had with previous attacks or if there is fever, pains in the loins, dysuria or a sudden increase in white cell excretion, antibiotics should be started at once, whether or not the urine contains organisms If the patient is intelligent she can be given some antibiotic to keep at home and to take at the first sign of a recurrence Sometimes recurrences are so frequent that it is best to give intermittent courses of antibiotics all the year round, either every few days, or for a week once a month, very occasionally it is necessary to give antibiotics every day throughout the year The urine must be cultured at regular intervals during treatment to check on the sensitivity of the organism During pregnancy, a woman known to suffer from chronic pyelonephritis should be given prophylactic antibiotics throughout

The choice of antibiotic depends on the sensitivity of the organism and the patient's reaction to its administration

Phenacetin Overdosage

Phenacetin is either taken alone or in combination with other analgesics, e g tab codeine co, which contains 250 mg of phenacetin per tablet The prolonged ingestion of phenacetin over several years can cause chronic renal failure

Pathology

The macroscopic appearances are the most characteristic and are due to the multiple loss of papillæ. Microscopically the lesion consists of a chronic inflammation of the interstitial spaces which is particularly marked in the medulla and papillæ. Tubules are eventually destroyed while the glomeruli tend to remain intact. When the changes in a papilla are sufficiently advanced it necroses, becomes detached from the medulla and is passed in the urine.

Clinical Findings

Four main groups of individuals are liable to take phenacetin in large amounts. The most understandable is that which consists of persons who suffer from some chronic painful disease, such as rheumatoid arthritis, for which analgesics offer some relief. Another group consists of workers such as watchmakers who are liable to headaches. In some Swiss factories it used to be customary for the firm to distribute phenacetin free of charge to its workers. A third group are compulsive analgesic consumers. They have no pain or headache and they obtain no overwhelming pleasure from the ingestion of phenacetin. Their habit has usually started for some trivial reason and they can be induced to stop without much effort. The last group is a remarkable one and was first described from Sweden, it provided the first conclusive evidence of the toxicity of phenacetin. A whole village became addicted to phenacetin. The drug became a symbol of friendliness and sociability. When a few people gathered together they would offer each other a phenacetin tablet as a preliminary to conversation, while those who were invited out to dinner would take their hosts a packet of phenacetin.

The ingestion of about 2 kg. of phenacetin (e.g. tab. codeine co. × 6 per day for four years) is associated with a substantial risk of developing renal failure. The patient may first present for some other complaint when it is found that he has proteinuria, or he may appear with renal colic with hæmaturia, or chronic renal failure and hypertension. The renal colic is caused by the passage of necrosed papillæ which can sometimes be recognised in the urine.

The diagnosis is made by asking the right questions. Apart from this the most characteristic findings are a sterile pyuria and pyelographic evidence of loss of papillæ.

Treatment

Most cases are due to self-administration. The incidence would therefore be considerably reduced if it were made illegal to buy phenacetin in any form without a prescription.

In the established case the most useful measure is to persuade the patient to stop taking any more phenacetin In those with well marked renal failure there is sometimes some improvement in function but the most striking result is that there is no further deterioration If the disease is far advanced, renal failure may progress to death of the patient in spite of stopping the phenacetin Nevertheless a few patients with creatinine clearances around 10 ml /min have survived

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23

POLYURIA

The functional disturbances which cause polyuria are (*a*) lack of circulating antidiuretic hormone (ADH) or (*b*) an inability of the kidneys to concentrate urine although ADH is present because of (1) impaired ability of the tubule to respond to ADH (2) a fault in the mechanism concerned with producing a hypertonic interstitial fluid in the medulla and (3) an increased solute output (i e an osmotic diuresis) It may be difficult or impossible in an individual patient to disentangle which of these abnormalities is responsible for polyuria The important point is that more than one abnormality may be present in any one form of polyuria This is best demonstrated if the clinical causes of polyuria are listed under the various disturbances mentioned (see below) When the clinical condition is due to more than one functional abnormality it is listed in italics under that abnormality which is considered to be the principal cause of the polyuria

POLYURIA DUE TO DIMINISHED CIRCULATING ANTIDIURETIC HORMONE (ADH)

1 Because of an impaired ability to secrete ADH

- (*a*) Persistent defect
  - (i) *Lesions of the supraoptico-hypothalamus i e diabetes insipidus*
- (*b*) Transient defect
  - (i) Compulsive water drinking
  - (ii) ? Potassium deficiency

2 Because of a diminished need to secrete ADH due to an increased intake of water due to increased thirst

- (*a*) *Compulsive water drinking*
- (*b*) *Potassium deficiency*
- (*c*) *Lesion of thirst centre*
- (*d*) Hypercalcæmia

POLYURIA IN SPITE OF ADEQUATE CONCENTRATIONS OF CIRCULATING ADH

1. ***Because of an impaired ability of the tubule "wall" to respond to ADH***
    - (*a*) Congenital.
        - (i) A single tubular lesion, i.e. *nephrogenic diabetes insipidus.*
        - (ii) One of several tubular lesions, i.e. *renal tubular acidosis, Fanconi's syndrome.*
    - (*b*) Acquired.
        - (i) Compulsive water drinking.
        - (ii) Diabetes insipidus.

2. ***Because of a fault in the mechanism concerned with producing a hypertonic interstitial fluid in the medulla***
    - (*a*) ? Due to an impaired sodium transport in the loop of Henle.
        - (i) Potassium deficiency.
        - (ii) Hypercalcæmia and hypercalcuria.
    - (*b*) ? Due to a disturbed flow of blood in vasa recta, or structural damage to loop of Henle.
        - (i) Chronic pyelonephritis.
        - (ii) Widespread gradual destruction of nephrons, i.e. most instances of chronic renal failure.
        - (iii) Hydronephritis.
        - (iv) Sickle cell anæmia.

3. ***Because of an increased solute output per nephron (osmotic diuresis)***
    - (*a*) Through a normal number of nephrons.
        - (i) *Glycosuria.*
        - (ii) *Salt diuresis following relief of urinary obstruction.*
    - (*b*) Through a greatly reduced number of nephrons.
        - (i) *Chronic renal failure.*

Polyuria due to glycosuria is easily diagnosed by a routine test of the urine.

The other causes of polyuria can be subdivided into those that are associated with a moderate rise in blood urea and in which the urine volume is usually only increased to about 3–4 litres per 24 hours, and those that have a normal or low blood urea, and in which the urine volume is usually above 5 litres per 24 hours (often up to 10–12 litres).

Those conditions in which there is a rise in blood urea and only a moderate rise in urine volume include chronic renal failure, potassium deficiency, some cases of hypercalcæmia, and renal tubular acidosis, while those with a normal blood urea and the excretion of large volumes of urine include diabetes insipidus, compulsive water drinking, some cases of hypercalcæmia, and familial nephrogenic diabetes insipidus

A *Polyuria with urine volume usually less than 3–4 l /24 hr and blood urea raised*	B *Polyuria with urine volume often greater than 5 l /24 hr and blood urea normal*
1 Chronic renal failure (p 165)	1 Diabetes insipidus
2 Potassium deficiency (p 198)	2 Compulsive water drinking
3 Hypercalcæmia (p 203)	3 Hypercalcæmia (p 203)
4 Fanconi s syndrome (p 214)	4 Familial nephrogenic diabetes insipidus

The disturbances included in Group A have been discussed in earlier sections *Those in Group B are discussed below, except for* hypercalcuria, which has been discussed on p 203

CAUSES OF POLYURIA IN WHICH THE URINE VOLUME IS USUALLY GREATER THAN 5 LITRES/24 HOURS AND THE BLOOD UREA IS NORMAL

Familial Nephrogenic Diabetes Insipidus

This is a rare sex linked condition which occurs in males and with such a marked familial incidence that sometimes there are several patients under the same roof with the same symptoms The onset of symptoms is during infancy or childhood Occasionally chronic *dehydration with plasma hypertonicity in infancy may lead to severe* and permanent mental retardation Investigation of entire families has shown that they may contain symptomless heterozygous female carriers, in whom there is a mild impairment of maximum concentrating capacity

The evidence that the primary defect is an inability of the tubules to utilise vasopressin is obtained by giving vasopressin intravenously In nephrogenic diabetes insipidus the amount of vasopressin that then appears unchanged in the urine is much greater than in normal subjects It must also be pointed out that microdissection of nephrons has revealed that in nephrogenic diabetes insipidus the proximal tubules are shorter than normal The relevance of this finding to the inability of the tubule to utilise vasopressin is not clear If, however, *the shortening results in an increased amount of glomerular filtrate* reaching the loop of Henle and the distal tubule it may be an additional cause for the hypotonicity of the urine.

The disease is characterised by an almost complete inability to raise the urine concentration above the concentration of plasma with either 5 units of vasopressin tannate in oil intramuscularly, or moderately severe fluid deprivation sufficient to cause a loss of up to 5 per cent of body weight; in both instances the urine usually remains around S.G. 1·004. If the vasopressin dosage is raised to toxic levels (i.e. 2 units of the aqueous solution intravenously), or the dehydration is so severe that it gives rise to distress and fever, the urine concentration may then rise to much higher levels; this is sometimes seen terminally in nephrogenic diabetes insipidus of infancy.

Treatment consists mainly in early recognition and the adequate administration of water. Infants also greatly benefit from a low electrolyte diet, for this produces a quicker return to normal plasma osmolality. Diuretics which cause much sodium loss such as frusemide or chlorothiazide can reduce the extent of the polyuria. They are useful for special occasions, but their prolonged administration may cause potassium deficiency. It is not known how they reduce the urine volume. It has been pointed out that this only occurs when the patient is in a negative sodium balance, and it has been suggested that this causes such an increased reabsorption of sodium from the proximal tubule that the quantity of tubular fluid which travels into the loop of Henle and emerges into the distal tubule as hypotonic fluid is greatly reduced.

Diabetes Insipidus

It has been mentioned above that diabetes insipidus is due to a diminished ability of the supraopticohypophyseal system to secrete ADH. This is usually an acquired defect associated with fracture of the base of the skull, tumours, infections and lipoid storage diseases. Not infrequently the cause is unknown. It is more common in men than in women. A few familial congenital cases have been described.

The onset of symptoms is usually gradual and, once polyuria and polydipsia have developed, the daily water exchange remains relatively constant. Sometimes 12–15 litres of fluid are ingested and excreted each day for many years; yet, in spite of the great disturbance to sleep, there may be no other symptoms or signs. Loss of weight, exhaustion and constipation occur if the urine volumes become astronomical, i.e. 20–30 litres a day.

Differential Diagnosis

The main difficulty in the differential diagnosis is to distinguish between diabetes insipidus and compulsive water drinking. Sometimes diabetes insipidus can be distinguished with relative certainty by finding *other evidence of structural disease in the area of the neurohypophysis*, or a diagnosis of compulsive water drinking can be inferred from the patient's disturbed mental state and previous history of psychiatric peculiarities Often the distinction between these two conditions has to be made following the administration of vasopressin, a period of fluid deprivation, and on an estimate of the plasma osmolality (see below)

Treatment

The administration of vasopressin immediately relieves the thirst and polyuria. The duration of the relief depends on the vasopressin preparation and on the tubular capacity to concentrate The effect of vasopressin tannate in oil, 5 units intramuscularly, should continue for 2–3 days, whereas the effect of lysine vasopressin spray wears off after 3–6 hours The spray is best carried about in case of an emergency; sometimes the effect of the vasopressin tannate in oil wears off with an embarrassing rapidity The disadvantage of vasopressin tannate in oil is that the sites of injection are apt to feel a little sore for 2–3 weeks The disadvantage of the nasal preparation is the occasional development of rhinorrhœa or asthma The incidence of such side effects with the synthetic lysine vasopressin spray, however, is much less than with the crude preparations of vasopressin snuff which used to be the only preparation available

Compulsive Water Drinking

This is a much more common condition than diabetes insipidus It is seen principally in middle-aged women. The onset of polydipsia and polyuria is often sudden and not infrequently it coincides with medical advice to drink more fluid (e.g for constipation) The quantity of water which is consumed is apt to vary erratically from one day to the next, and frequently there is also a slow periodicity, with relapses and remissions varying from several weeks to months Hysterical manifestations and depression are a part of the syndrome, and there is nearly always a long previous history of psychological disturbances, occasionally these patients are discovered to be magnifying the extent of their polyuria by pouring jugs of water into the bedpan

A diagnosis of compulsive water drinking is usually suspected from the history and appearance of the patient, and often it is soon apparent that polydipsia and polyuria are the least of the patient's troubles The differential diagnosis between diabetes insipidus and compulsive water drinking is discussed below

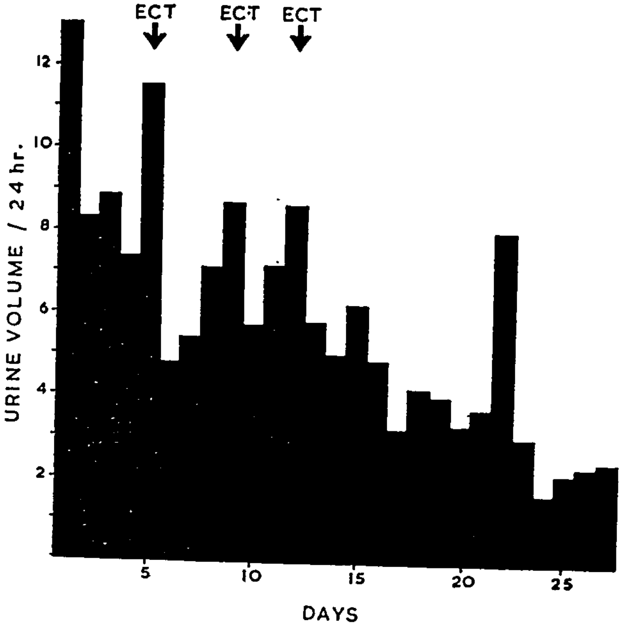

FIG. 23.1. The effect of electro-convulsive therapy (ECT) on a patient with compulsive water drinking and severe depression.

Treatment

The only treatment which is likely to succeed is one that controls the particular psychological disturbance involved. Sometimes reassurance and encouragement are sufficient. Occasionally a rest in hospital will produce marked improvement and, if such a remission coincides with the administration of vasopressin, an erroneous diagnosis of diabetes insipidus may be made. Usually stronger measures have to be employed, such as electro-convulsive therapy for the depression (Fig. 23.1) and continuous narcosis for hysteria. Substantial remissions may be induced but the tendency to relapse is very great.

THE USE OF VASOPRESSIN AND FLUID DEPRIVATION TO DISTINGUISH BETWEEN DIABETES INSIPIDUS AND COMPULSIVE WATER DRINKING

As diabetes insipidus is due to a persistent defect in the ability to secrete ADH because of an abnormality of the neurohypophysis, and compulsive water drinking is simply an increased intake of fluid because of a mental abnormality, it should be possible to distinguish the two conditions by estimating the concentration of antidiuretic hormone in the blood during a period of fluid deprivation. It should be low in diabetes insipidus and high in compulsive water drinking.

Unfortunately, there is as yet no reliable method of estimating the concentration of circulating ADH in the plasma directly Its presence has to be deduced by observing changes in urine flow and urine concentration For this reason, diabetes insipidus and compulsive water drinking have to be distinguished by (1) estimating and comparing the kidney's ability to concentrate the urine following the administration of vasopressin and after a period of fluid deprivation, (2) by observing the generalised effects of a long lasting vasopressin preparation, and (3) estimating the osmolality of the plasma

Urine Concentration after Vasopressin Administration, and Fluid Deprivation

Vasopressin is given when the patient is not being deprived of fluid to determine the efficiency of the kidney to concentrate the urine, and fluid deprivation is used to test the ability of the neurohypophysis to secrete ADH It is logical to do these tests in this order, for the presence of ADH following fluid deprivation is inferred from the rise in the concentration of the urine, this, in turn, is dependent on the tubule's ability to respond to ADH The interpretation of these two tests depends on the fact that when the ability to secrete ADH *is normal the concentration of the urine after fluid deprivation is* greater than after the administration of vasopressin

Vasopressin is given at a time when the patient's consumption of water is perfectly free and uninhibited, it is administered either intravenously as 100 m Units in 20 seconds followed by 5 m Units/min thereafter for one hour, or intramuscularly as (1) vasopressin tannate in oil, 5 units, or (2) aqueous vasopressin 2 5 units The test is most accurately performed with the first technique, but it is more convenient to use vasopressin tannate in oil, for it is then unnecessary to catheterise the patient, nevertheless vasopressin tannate in oil may be dangerous for patients with compulsive water drinking (p 313)

A *period of fluid deprivation stimulates* ADH production because of the negative balance of water that results The duration of such a period therefore is of secondary importance For instance, a period of 12 hours' fluid deprivation is a stronger stimulus to ADH production in a polyuric patient unable to concentrate the urine, and who therefore excretes 3 to 5 litres of water, than is a 24-hour period of fluid deprivation in a normal person who only loses 1 litre The most satisfactory method is to be guided by the weight that is lost during fluid deprivation, and to estimate the urine concentration after the loss of 3 to 5 per *cent of the initial weight If greater losses are allowed the urine may* become concentrated by mechanisms other than the neurohypophyseal secretion, and the test becomes pointless

Theoretically the result of these two tests in diabetes insipidus and compulsive water drinking should be as follows: patients with diabetes insipidus should concentrate their urine normally with vasopressin but not with fluid deprivation, whereas patients with compulsive water drinking should concentrate the urine normally with both vasopressin and fluid deprivation. Unfortunately, though this is frequently true, the situation is not always so straightforward.

Results of Vasopressin and Fluid Deprivation Tests in Diabetes Insipidus (Fig. 23.2). Patients with diabetes insipidus are, indeed, unable to concentrate their urine following fluid deprivation and able to do so normally after vasopressin. The former becomes more evident if vasopressin is given at the end of the period of fluid deprivation, for there is then a rise in urine concentration to a level well above that obtained with vasopressin alone. Occasionally the response to vasopressin alone, though considerably greater than that following fluid deprivation, is still below normal.

Results of Vasopressin and Fluid Deprivation Tests in Compulsive Water Drinking (Fig. 23.2). These patients may respond in a variety

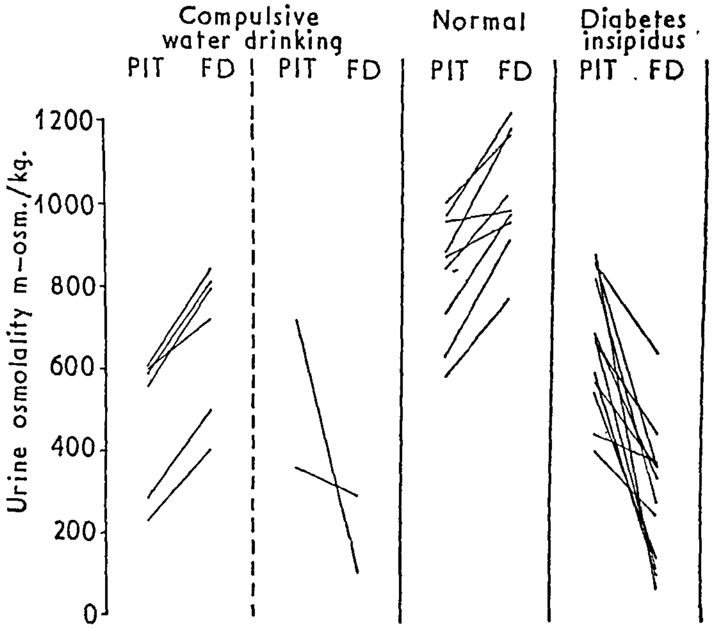

FIG. 23.2. Test of neurohypophyseal integrity by fluid deprivation and vasopressin. The urine osmolality after intravenous aqueous vasopressin (PIT) and after fluid deprivation (F.D.), in compulsive water drinking, normal individuals and in diabetes insipidus; each line represents one subject. (Barlow and de Wardener, 1959, *Quart. J. Med.*)

of ways and the multiplicity of their responses is very confusing The following responses are seen·

1 The kidney's ability to concentrate the urine following vasopressin and fluid deprivation is normal, *i e urine concentration rises to* levels found in normal individuals and, what is more important, *the concentration after fluid deprivation is greater than after vasopressin*

This indicates that both tubular function and the ability to secrete antidiuretic hormone are normal Such a response is only found in patients whose daily urine volume is less than 5 litres

2 The kidney's ability to concentrate the urine following both vasopressin and fluid deprivation is impaired, but the concentration after fluid deprivation is greater than after vasopressin

This indicates that tubular function is impaired but the ability to produce ADH is normal In these patients the urine concentration after vasopressin may be around S G 1 010 and after fluid deprivation S G 1 014

3 The kidney's ability to concentrate the urine following vasopressin is normal, but following fluid deprivation the concentration is considerably less than that following vasopressin (i e the response to the two tests is the same as in diabetes insipidus)

This indicates that tubular function is normal, but that there is an inhibition to ADH production which is not overcome by fluid deprivation It may be difficult to differentiate such a patient from one suffering from diabetes insipidus, particularly if the aqueous vasopressin preparation has been used. If vasopressin tannate in oil has been given the distinction is usually easier (see below)

4 Finally, the kidneys are unable to concentrate the urine following vasopressin, but the concentration after fluid deprivation is even less

This indicates that there is a combination of tubular impairment and inability to secrete ADH These are identical responses to *those obtained in diabetes insipidus They demonstrate an ability to* inhibit ADH secretion in spite of fluid deprivation, presumably due to the emotional stress of the test This conclusion is confirmed by obtaining a normal response to fluid deprivation after treating the patient with some suitable psychotherapeutic manœuvre

Discussion It is not at all clear why the kidney's ability to concentrate the urine following vasopressin is impaired in both diabetes insipidus and compulsive water drinking A similar impairment can be demonstrated in normal subjects drinking 8–12 litres of water a day (Fig 23 3) It would appear to be unrelated to the expansion of the extracellular fluid or blood volume It is more likely to be due to some change in the renal medulla consequent upon the increased rate of flow of hypotonic urine. In a patient with diabetes insipidus the ability to concentrate the urine takes several days or weeks to return to normal after starting treatment with vasopressin.

It is interesting to note that patients with long-standing polyuria and polydipsia excreting hypotonic urine may also have a reversible impairment in their ability to acidify the urine. To the unwary this combination of polyuria and polydipsia with an impaired ability to concentrate and acidify may suggest a diagnosis of renal tubular acidosis secondary to renal disease. This is a diagnostic trap into which only the sophisticated who measure these various tubular functions may fall. On the other hand, they are the ones best qualified to interpret these findings correctly.

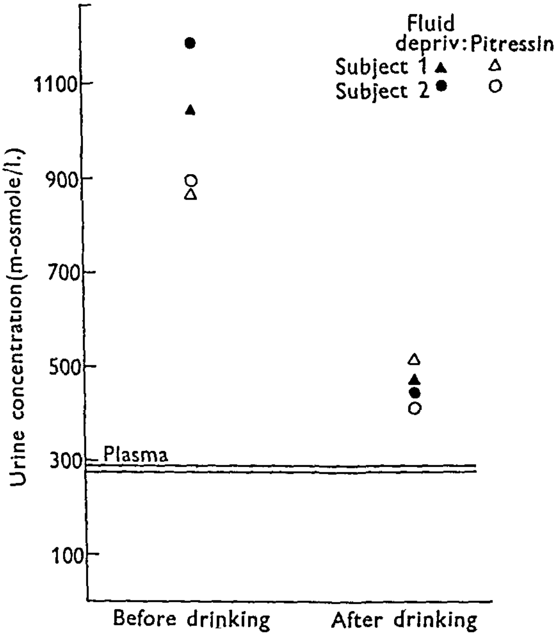

Fig. 23.3. Urine concentrations following the intravenous administration of vasopressin, and after a 26-hour period of fluid deprivation, before and at the end of drinking about 10 l. of water a day for 11 days. The plasma osmolarity varied between the limits indicated by the two parallel horizontal lines. (de Wardener and Herxheimer, 1957, *J. Physiol.*)

The patient's ability to secrete ADH is sometimes tested by other means than fluid deprivation. For instance, the supraopticohypophyseal system can be stimulated by intravenous nicotine, or by suddenly raising the plasma osmolality with an infusion of hypertonic saline. Nicotine acid tartrate (3 to 6 mg.) is given intravenously; it is only effective if it induces severe nausea and vomiting, but even if these unpleasant symptoms are produced some normal subjects may fail to respond The hypertonic saline test is performed by infusing 2 5 g per 100 ml saline at a rate of 0 25 ml /kg of body weight per minute, an hour after the oral ingestion of 20 ml /kg of water The urine flow should fall, but occasionally the water diuresis is replaced by a saline diuresis and the urine flow does not change materially (particularly in hypertensive women) Another disadvantage is that *in elderly patients the large infusion of saline may precipitate heart* failure Neither of these two manœuvres gives as much information as a properly controlled period of fluid deprivation, which is in any case a more physiological stimulus to ADH secretion

General Effects following the Administration of a Long-Acting Vasopressin Preparation

If a patient suffering from compulsive water drinking is given a long acting vasopressin preparation, i e vasopressin tannate in oil there is a considerable decrease in urine flow even if the tubule s capacity to concentrate is seriously impaired[*] (see above) But usually thirst continues unabated, the intake of water exceeds the output, and overhydration develops There is abdominal distension, headache, drowsiness, and sometimes nausea and vomiting In striking contrast, therefore, to patients suffering from diabetes insipidus, cases of compulsive water drinking complain of the vasopressin injections, often with much vehemence and bitterness Occasionally, both the patient and his attendants are unaware that the onset of nausea, headache and drowsiness is related to the administration of vasopressin Instead these symptoms are considered to be additional evidence in favour of an intracranial lesion in the vicinity of the neurohypophysis, and therefore of a diagnosis of diabetes insipidus

Plasma Osmolality

The plasma osmolality of patients suffering from diabetes insipidus and compulsive water drinking is compared in Fig 23 4 with that of normal subjects The mean osmolality in diabetes insipidus (295 ± 15 m Osm /kg) is significantly higher than in the normal subjects (280 ± 6 m Osm /kg), whereas in compulsive water drinking (269 ± 14 m Osm /kg) it is significantly lower These findings are in keeping with the ætiology of the two conditions In patients with diabetes insipidus the initial disturbance is polyuria and the excessive drinking is a normal response to the contraction and concentration of body

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[*] Vasopressin can lower the urine flow from 10 to 3 ml /min. without the concentration of the urine rising above S G 1 012. higher concentrations only occur at lower urine flows

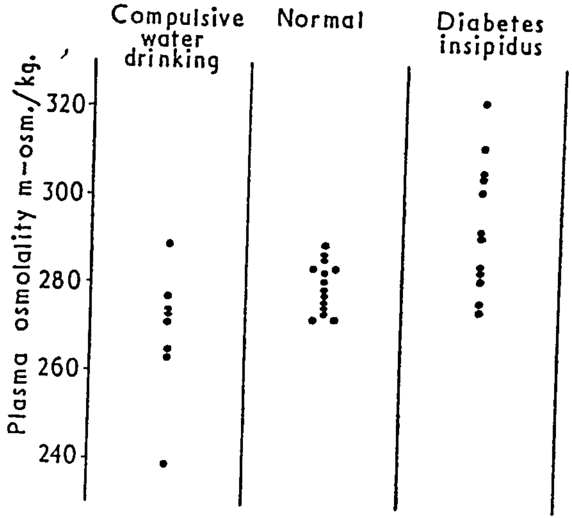

FIG. 23.4. Plasma osmolality in compulsive water drinking in normal subjects and in diabetes insipidus. (Barlow and de Wardener, 1959, *Quart. J. Med.*)

fluids, whereas in compulsive water drinking the initial disturbance is excessive drinking and the polyuria is the normal response to expansion and dilution of body fluids. There is a considerable overlap between the groups, but it appears that if the plasma osmolality of a patient with polyuria is greater than 290 m.Osm./kg. the diagnosis is likely to be diabetes insipidus, and if it is less than 275 m.Osm./kg. it is more likely to be compulsive water drinking.

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24

THE KIDNEY, GLYCOSURIA AND DIABETES MELLITUS

Glycosuria

IT has been pointed out in Section 5 that the quantity of glucose which passes through a glomerulus in one minute is the product of the filtration rate and the plasma glucose, and that normally the urine is free from glucose because this filtered glucose is reabsorbed in the proximal tubule. The rate at which glucose can be reabsorbed, however, is limited, and at normal glomerular filtration rates many of the tubules cannot reabsorb a greater amount than that which is delivered to them when the plasma glucose is about 170 mg. per 100 ml. The appearance of glucose in the urine therefore denotes that either: (1) a normal tubular reabsorbing capacity for glucose has been exceeded by an increased rate of delivery through the glomerulus; or (2) a reduced reabsorbing capacity of some, or most, of the tubules has been exceeded, though the rate of delivery is normal.

Glycosuria is never due to an increased glomerular filtration rate, so that when the tubular capacity to reabsorb glucose is normal the appearance of glucose in the urine is due to hyperglycæmia, as in diabetes, thyrotoxicosis and Cushing's disease, or following a gastro-enterostomy when there is an excessively rapid intestinal absorption of glucose.

Glycosuria associated with a diminished tubular reabsorptive capacity and a normal blood glucose is often a benign familial condition and is known as *renal glycosuria* (the condition is also known as "renal diabetes" and "pseudorenal diabetes," names which only confuse). If the reabsorbing capacity of only a few of the tubules is abnormal an estimation of the total capacity of the kidneys to reabsorb glucose (Tmg) may be within normal limits; but when more tubules are involved the total capacity to reabsorb glucose is reduced; familial renal glycosuria may be associated with either of these findings.

It is clear that when there is glycosuria the simplest way to differentiate between hyperglycæmic glycosuria, and renal glycosuria is to estimate the concentration of blood glucose. The blood should be taken at the midpoint of a short urine collection period, preferably during a fast If this test is not decisive a glucose tolerance test should be done

There are three other variations on this theme of glomerular supply and tubular reabsorption of glucose which are clinically important

1 If, in a patient suffering from diabetes *and* renal glycosuria, *insulin dosage is being adjusted according to the output of glucose in the urine*, hypoglycæmia may be induced This often occurs in pregnant diabetics

2 Very occasionally, contraction of the extracellular fluid space in diabetic acidosis may cause such severe renal vasoconstriction and fall in glomerular filtration rate that, though there is hyperglycæmia, the amount of glucose being delivered to the tubule may still be within its reabsorbing capacity, and no glucose appears in the urine (p 79)

3 Finally, there are those rare cases of glycosuria associated with a normal blood sugar in which diminished tubular capacity to reabsorb glucose is not an isolated benign functional lesion, but is only one of many similar but more serious abnormalities of tubular function, i e Fanconi's syndrome (p 214)

Diabetes Mellitus

The following renal disturbances occur

1 Disturbances of renal function in the absence of ketosis
2 Disturbances of renal function during ketosis
3 Diabetic nephropathy
4 Pyelonephritis

Disturbances of Renal Function in the Absence of Ketosis

The glycosuria of diabetes is secondary to hyperglycæmia But its extent may give a misleading impression of the height of the blood glucose, for patients with diabetes often have renal glycosuria, and glycosuria may therefore be present when the blood glucose is normal Paradoxically the glucose Tm (p 79) is *raised* in diabetes, the cause of this teleologically reasonable phenomenon is not known, it tends to subside after the administration of insulin The simultaneous presence of renal glycosuria and a raised glucose Tm is presumably due to a splaying out of the individual nephrons capacity to reabsorb glucose

The osmotic diuresis provoked by the glycosuria causes many of the characteristic features of diabetes mellitus, for it is responsible for a high urinary excretion of water, sodium and potassium, which gives rise to polyuria, thirst and lassitude

As glucose is a dense molecule, urine that contains glucose will tend to have a higher specific gravity than its colour would suggest, i e a pale urine may be found to have a specific gravity of 1 026

Disturbances of Renal Function during Ketosis

The urine in diabetic ketosis is acid and is characterised by an increased excretion of glucose, water, sodium, potassium and ketones, including β-hydroxybutyric acid. In severe cases there is metabolic acidosis, severe dehydration with a raised plasma sodium concentration, and a contraction of the extracellular fluid volume and the blood volume. The metabolic acidosis is caused principally by an accumulation of ketones due to an increased rate of ketone production, and ultimately there may also be some impairment in the kidney's ability to excrete hydrogen ions and ammonia. This impairment is due to both the sodium and potassium deficiencies which follow a prolonged osmotic glucose diuresis (Fig. 24.1). Potassium deficiency diminishes the tubule's ability to form a urine of maximum acidity which reduces the transfer of ammonia from the tubule cell to the tubule lumen. And severe sodium deficiency decreases the tubule's capacity to form ammonia. In consequence the acidosis is increased and the ketones in the urine are excreted with sodium and potassium ions, thus aggravating their deficiencies. Although there is an overall potassium deficiency there is often a shift of potassium out of the cells so that the concentration of plasma potassium tends to be raised, a phenomenon which is reversed by the administration of insulin.

The loss of salt and water causes contraction of the extracellular fluid space and the blood volume; renal vasoconstriction follows and there is a reduction in renal blood flow and glomerular filtration rate, with a rise in blood urea. The fall in glomerular filtration rate also reduces the urinary excretion of ketones, and this further aggravates the metabolic acidosis. Occasionally, in very severe cases, filtration may fall to such a low rate that all the glucose *and ketones* which are filtered are reabsorbed by the tubules and none appear in the urine; this may cause considerable diagnostic confusion. The fall in glomerular filtration is also due in part to potassium deficiency, and this probably accounts for the slow recovery of renal function that sometimes follows the treatment of diabetic ketosis with only saline and insulin.

Acute renal failure with acute tubular necrosis may occur in the most severe cases.

Treatment

Insulin and antibiotics are given first, but to improve renal function it is essential to correct rapidly the negative sodium, water and potassium balances. Large quantities of isotonic sodium chloride and sodium bicarbonate (p. 197) are administered intravenously, and when the blood glucose has begun to settle, 5 per cent glucose is also given. It

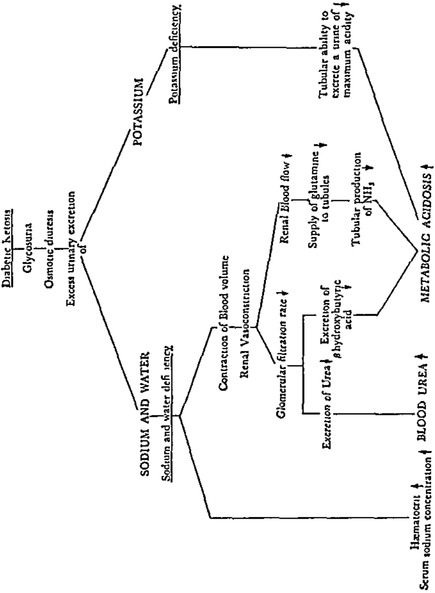
Diabetic ketosis
Glycosuria
Osmotic diuresis
Excess urinary excretion of
SODIUM AND WATER
POTASSIUM
Potassium deficiency
Sodium and water deficiency
Contraction of Blood volume
Renal Vasoconstriction
Renal Blood flow ↓
Glomerular filtration rate ↓
Supply of glutamine to tubules ↓
Tubular production of NH_3 ↓
Excretion of β hydroxybutyric acid ↓
Excretion of Urea ↓
Tubular ability to excrete a urine of ↑ maximum acidity ↓
METABOLIC ACIDOSIS ↑
BLOOD UREA ↑
Hæmatocrit ↑
Serum sodium concentration ↑

Fig 24 1 Renal disturbances and their consequence in diabetic ketosis

is unwise to give potassium solutions intravenously until, or unless, the urine flow is brisk, and the acute phase of the ketosis has passed, for the concentration of plasma potassium is often very high (see above)

These measures (except for potassium administration) are undertaken even in the presence of acute oliguria, for though they may be too late to prevent the development of acute tubular necrosis, their administration may limit the extent of the damage. Sometimes the blood pressure is very low, when it must be raised with blood transfusions, for a combination of renal vasoconstriction and hypotension is particularly likely to cause complete renal ischæmia and necrosis (p. 145). In most instances the blood pressure rises and the urine flow returns within a few hours of giving saline, and it becomes clear that acute tubular necrosis has not occurred.

Diabetic Nephropathy

Widespread vascular abnormalities occur frequently in longstanding diabetes. They differ from the common forms of hypertension or atheromatous vascular changes and are situated in the retinal veins and arteries, the arteries to the peripheral nerves, and the renal arteries and capillaries.

Pathology

The kidney may be of normal size or even a little larger than normal. The vascular lesions involve the glomerular capillaries and both the afferent and efferent arterioles. Their distribution may be widespread or focal, and the capillary lesions tend at first to involve only one part of a glomerulus.

In the glomeruli there are two principle lesions. One consists of globular, eosin staining, amorphous masses of basement membrane material focally distributed within the glomeruli. The other consists of lobular stalk thickening with eosinophilous material. The first lesion is known as the Kimmelstiel-Wilson lesion but it is probable that both are different stages of the same process for the globular lesions occur mainly after the diffuse lesions are well established. The globular masses tend to occur at the periphery of one of the capillary loops, and eventually, as they enlarge and multiply, they obliterate the tuft (Fig. 24.2). The capillaries which give rise to these excrescences are dilated and appear to be obstructed. The changes associated with lobular stalk thickening may also obliterate the glomerulus, and may do so without the typical Kimmelstiel-Wilson lesion being present. Occasionally there are also some exudative lesions of protein-like substance containing high quantities of fat usually originating and attached to Bowman's capsule. Very rarely the appearances are identical to those of membranous glomerular nephritis, with a diffuse even thickening of the glomerular capillary walls.

The electron microscope shows that the basement membrane is enormously thickened and that the globular masses at first lie in the endothelial cells. The epithelial cells often have disorganised foot processes; sometimes these are no longer distinct and instead are converted into large islets of cytoplasm covering the outer surface of the capillary

The *glomerular lesions are usually found in association with gross* thickening of the afferent and efferent arterioles (mainly the afferent) of the glomeruli involved The arteriolar walls keep their sharp outline

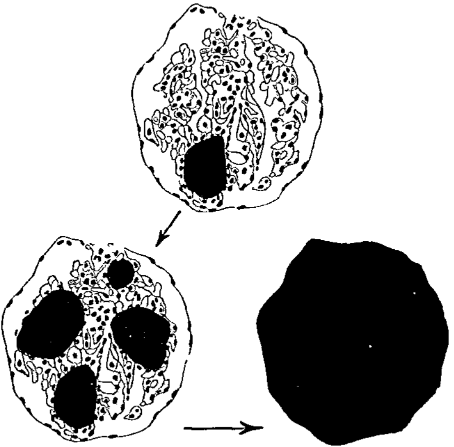

Fig 24 2 Diabetes (Kimmelstiel Wilson lesions) Schema illustrating the *peripheral distribution in the glomerulus of the characteristic deposits of* eosin staining material and how eventually they may entirely fill the glomerulus The non specific lesions which also occur in diabetic nephropathy (see text) are not shown

(unlike the appearances in fibrinoid necrosis), but are widened by some material which stains a deep and vivid pink with hæmatoxylin and eosin, the composition of this substance is not known, it is not collagen or basement membrane like material

The tubules show similar changes to those found in persistent glomerular nephritis, and very occasionally the proximal tubules contain large quantities of glycogen. The interstitial tissues contain varying collections of chronic inflammatory cells in proportion to the number of glomeruli which are disintegrating.

Finally, the changes of hypertension and chronic or acute pyelonephritis are frequently found superimposed upon those just described.

Clinical Features

The first sign is proteinuria. It develops in most patients who have had the disease more than 10 years. There is a disputed claim that good control of the blood sugar with insulin and dietary measures lessens the incidence. This is unlikely to be an important factor for there is increasing biopsy evidence that the lesions can be present before the onset of glycosuria. Young males are particularly prone to develop diabetic nephropathy, though in absolute numbers most of the patients are middle-aged and elderly women.

At first the proteinuria is often intermittent, but gradually it becomes persistent and increases in extent. Occasionally there is a nephrotic syndrome. Retinal, peripheral nerve lesions and, in the older patients, severe atheroma, develop at the same time as the renal lesions. Patients over 50 years of age usually present with hypertension or peripheral arterial disease.

The average duration of survival after the onset of proteinuria is about five years; it is longest in the young. Death is rarely caused by diabetic nephropathy itself except in the young who may die of chronic renal failure or of an infection complicating a nephrotic syndrome. The majority of patients succumb to coronary thrombosis, hypertensive cardiac failure or cerebrovascular accidents before the renal lesions are sufficiently advanced to produce any substantial changes in renal function.

Chronic renal failure associated with the classical lesions of diabetes has been found in patients who have never had glycosuria and in whom the diagnosis of diabetes has not been made. It is probable that in some of these patients, owing to a combination of a low glomerular filtration rate and a greatly increased ability to reabsorb glucose, there was no glycosuria, though there may have been hyperglycæmia. In a few patients the blood glucose have been measured and found to be normal, though at post-mortem there was, in addition to the characteristic diabetic renal lesions, widespread hyalinisation of the islets of Langerhans.

Relationship between Clinical and Structural Features. Electron microscopy studies on rneal biopsies from diabetic patients are beginning to show that the changes in the glomerular basement membrane probably precede the onset of proteinuria by several years.

It has also been established that electron microscopy abnormalities appear about five years after the clinical onset of diabetes, whereas light microscopy changes begin to be obvious after 10 years The histological changes are the same when the diabetes follows pancreatitis or hæmochromatosis

The extent of the proteinuria is greatest with severe structural changes, otherwise there does not appear to be any close relation between the histological appearances and renal function Occasionally there may be well-marked histological changes without proteinuria or impairment of renal function When light microscopy lesions are evident it is usual to be able to discern diabetic retinal lesions with an ophthalmoscope This relationship is so close that the finding of retinal changes is a good indication that renal changes are present whether or not there is proteinuria

It is important, though confusing, to point out that clinically it is impossible to predict the presence or absence of Kimmelstiel Wilson lesions Not infrequently these specific lesions will be found in patients who have never had proteinuria or other evidence of renal disease Many diabetic patients dying from renal failure subsequent to a nephrotic syndrome may not show the characteristic focal lesion though all will have the diffuse lesions

Treatment

Recently there have been a few claims that the vascular lesions regress and that proteinuria ceases following hypophysectomy Even so, it is difficult to advise a patient to have such an operation at the onset of his symptoms, later, when there is blindness or renal failure the lesions are likely to be irreversible Perhaps in the future it may be possible to inhibit anterior pituitary function by some less irrevocable and dangerous method. It has been claimed that as the nephropathy progresses certain patients require less insulin

Pyelonephritis

Diabetics are liable to infections in any site, and the kidneys are no exception Acute and chronic pyelonephritis often accompany the renal vascular changes described above Acute pyelonephritis is always accompanied by diabetic acidosis

Acute necrotising papillitis occurs more frequently in diabetes than in any other condition, but is seldon seen

Treatment

Whereas the vascular lesions are untreatable the infections can be controlled It is of the greatest importance in diabetics to be always on the look out for urinary infections, for if they are overlooked the combination of infection and vascular damage is rapidly lethal. Renal infections should be treated in the way outlined earlier (p. 296).

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RENAL DISTURBANCES IN PREGNANCY

1. Physiological changes:

    Renal blood flow and glomerular filtration rate.
    Lactosuria and glycosuria.
    Orthostatic proteinuria.
    Ureteric and pelvic dilatation.

2. Renal infections.
3. Renal changes associated with toxæmia of pregnancy and eclampsia.
4. Acute renal failure.
5. Pregnancy and pre-existing chronic renal disease.
6. The incidence of other renal diseases during pregnancy.

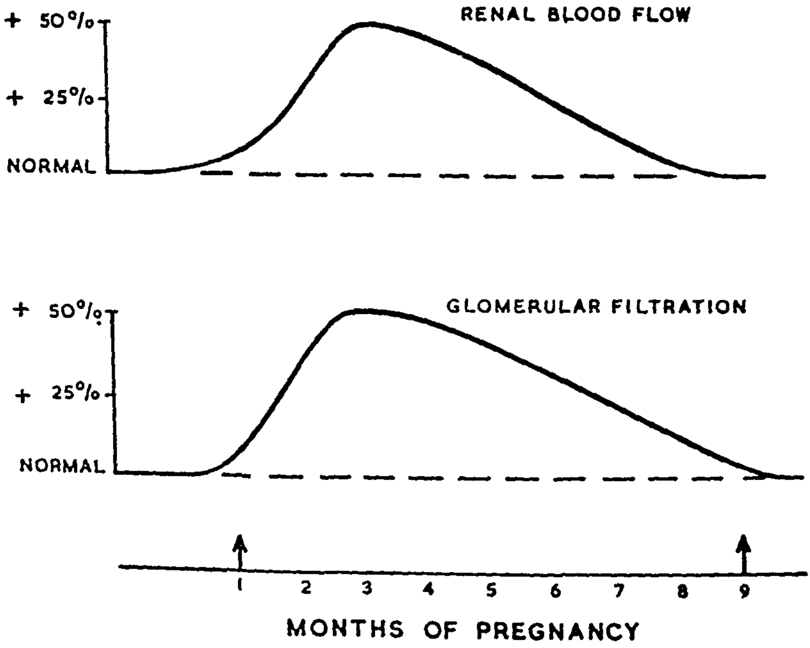

FIG. 25.1. Schema of the changes in renal blood flow and glomerular filtration rate which take place during pregnancy.

PHYSIOLOGICAL CHANGES

Renal Blood Flow and Glomerular Filtration Rate

In early pregnancy there is a substantial rise in renal blood flow and glomerular filtration rate, and by the fourth month both have increased by about 40 per cent Subsequently the renal blood flow gradually subsides, and by the end of the eighth month it has returned to normal Glomerular filtration rate follows a similar pattern except that some increase remains until the end of pregnancy (Fig 25 1)

The increase in glomerular filtration rate together with the diminished protein breakdown of pregnancy cause the blood urea to be considerably lower than normal e g 15 mg per 100 ml Unless this increase in glomerular filtration rate and fall in blood urea is appreciated a false impression of renal functional efficiency during pregnancy may be held Either an underlying renal disease is unsuspected because the filtration rate and blood urea are within normal (i e non pregnant) limits, or a sudden deterioration in renal function after pregnancy is erroneously considered to be evidence that pregnancy has injured the kidneys If during pregnancy the glomerular filtration rate is lower than the "non pregnant" normal rate, or the blood urea is raised above the normal ' non pregnant" concentration, it is evidence of considerable impairment of renal function, and perhaps extensive structural damage

Glycosuria and Lactosuria

Most women during pregnancy excrete an increased quantity of both glucose and lactose Glycosuria is due to a lowered renal threshold for glucose reabsorption Lactosuria is simply related to the presence of lactose in the mother's blood as it is not reabsorbed by the tubules all that is filtered through the glomerulus appears in the urine

After delivery glycosuria rapidly disappears and there is an increase in both the incidence of lactosuria and the amount that is excreted

At one time glycosuria after the oral ingestion of glucose was suggested as a test of pregnancy

Orthostatic Proteinuria

The incidence of orthostatic proteinuria varies considerably, some reports state that it is as high as 20 per cent It is probably caused by (1) an exaggeration of the normal mechanism for orthostatic proteinuria, i e a lordosis which rotates the liver forwards, thus compressing the inferior vena cava and causing a rise in renal venous pressure, and (2) uterine compression of the left renal vein as it crosses the midline The first mechanism causes protein to be excreted through both ureters, whereas with the second, protein is present only on the left side. In order, therefore, to distinguish orthostatic from other causes of proteinuria, the urine should be tested for protein, after the patient has been lying on her side.

Ureteric and Pelvic Dilatation

After the third month of pregnancy the ureters and renal pelves are usually dilated. Initially this is due to a ureteric and pelvic atony, possibly caused by hormonal changes accompanying pregnancy. Paradoxically the atony is associated with hyperplasia of the ureteric muscles; there is also an increase in the connective tissue within the ureteric walls. Later, as the uterus enlarges, it compresses the ureters at the pelvic brim; this mechanical obstruction is superimposed upon ureteric atony and the combination results in considerable ureteric dilatation. The ureters and pelves may contain more than 100 ml. of urine. It is interesting that during this period of ureteric dilatation there is no vesico ureteric reflux. Normally the uterus is tilted towards the right side and, in consequence, it is usual to find the ureteric dilatation on the right to be greater than on the left. After delivery ureteric dilatation gradually subsides in about three months. These changes are more marked in primigravidæ than in multiparæ. They are probably due to the increased concentrations of circulating eostrogens. Male rats given diethylstilbœstrol develop similar changes in their ureters to those seen in pregnant female rats, and at the same time their susceptibility to renal infection also rises.

RENAL INFECTIONS

Acute pyelonephritis* is the most common complication of pregnancy. It occurs in about 2 per cent of all pregnancies and is responsible for a great deal of discomfort and distress, a few immediate deaths both of the mother and the fœtus, and an unknown number of deaths many years later.

Ætiology

About three-quarters of all cases of acute pyelonephritis of pregnancy occur in the 5 to 8 per cent of women who have *persistent* bacteruria throughout pregnancy. Unfortunately it is not possible to identify this group by any means other than performing a quantitative urine culture. Nearly all patients are asymptomatic.

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* Obstetricians sometimes call the usual type of acute renal infection in pregnancy an acute pyelitis, and reserve the term acute pyelonephritis for those extremely severe infections with gross impairment of renal function which are usually due to a staphylococcal organism. This is a misleading use of the English language.

Bacteriuria is not related to previous catheterisation, past symptoms of urinary tract disease, or white cell excretion rate, and it occurs equally among women with or without anæmia The incidence of acute pyelonephritis in women with previously sterile urine often follows catheterisation of the bladder during or shortly after delivery

The remarkable severity and persistence of pyelonephritis in pregnancy is probably due to the dilatation, atony and compression of the ureters (see above)

Clinical Features

The incidence of acute pyelonephritis begins at the fourth month and continues well into the puerperium Much of the incidence in the puerperium is due to catheterisation About 15 per cent of women have some difficulty in initiating micturation in the first few days of the puerperium because of episiotomies, prolonged labour, etc They are liable to be catheterised in order to relieve overdistention of the bladder Symptomatically the infection is either bilateral or, when unilateral, it is usually on the right side The physical signs and symptoms have been described on p 287 Mild cases only complain of backache, they may admit to occasional feverish symptoms or pain on passing water with some reluctance, considering that such symptoms are normal in pregnancy Some attacks may be associated with such severe vomiting that the patient is thought to be suffering from hyperemesis gravidarum

As in all forms of renal infection the most helpful diagnostic features are rigors, fever, tenderness in the costo vertebral angles, an increased number of white cells and a significant number of organisms in the urine

An intravenous pyelogram should only be performed if there is reason to believe that there is a calculus, an ectopic kidney, or there are recurrent infections difficult to control The number of films should be strictly limited, for recent statistical evidence suggests that acute leukæmia in children may follow fœtal exposure to diagnostic X rays A unilateral *left-sided* infection is particularly likely to be due to some additional disturbance of the renal tract such as a calculus

Differential Diagnosis

It is important to stress that often in acute pyelonephritis of pregnancy there are no lower urinary symptoms If therefore a pregnant woman has an unexplained fever the urine should be cultured immediately On the other hand it is now well established that over 70 per cent of pregnant women who do complain of lower urinary symptoms have a sterile urine

Treatment

Prophylactic. This is a contentious point. It is possible by routinely culturing the urine of all patients at the beginning of pregnancy, to identify those among whom most of the attacks of acute pyelonephritis will occur. If the urine of these women is sterilised with nitrofurantoin 100 mg. at night throughout pregnancy the incidence of acute pyelonephritis is virtually eliminated. This procedure does not harm the fœtus or give rise to an increased incidence of neonatal jaundice.

It has been proposed that this prophylactic manœuvre should be undertaken as a routine antenatal service, for it has been claimed that it not only lowers the incidence of acute pyelonephritis but that it also substantially diminishes the incidence of toxæmia of pregnancy and the peri-natal mortality rate. There is no doubt that at one time this was true in certain underdeveloped parts of Boston, Mass., and the West Indies which contained an impoverished population in which the overall incidence of toxæmia of pregnancy and prematurity were extremely high; in those women who had persistent bacteruria it was even higher. In other parts of the world, however, such as London and Aberdeen the incidence of toxæmia and prematurity is much lower and is no greater in untreated bacteruric women than in women with sterile urine. Sterilising the urine of women with bacteruria in London and Aberdeen therefore cannot lower the incidence of toxæmia or the prematurity rate. In Melbourne the overall incidence of prematurity is low and yet it is considerably greater among the bacteruric women, nevertheless, sterilising the urine of bacteruric women does not lower the incidence of prematurity. It now appears therefore that unless the overall incidence of toxæmia and prematurity is high, such as in Boston, Mass., or the West Indies the only benefit to be obtained from treating asymptomatic proteinuria of pregnancy is to reduce the incidence of acute pyelonephritis.

Some authorities consider that this is not a sufficient return for the expense and inconvenience involved in culturing the urine of all pregnant women. They point out that nowadays acute pyelonephritis is easily treated and rarely leads to protracted admission to hospital. Others point out that (1) the expense and inconvenience of culturing the urine can be reduced by certain simplifications; (2) that acute pyelonephritis is sometimes followed by recurrent ill health for some months after delivery; and (3) that if acute pyelonephritis is not prevented, it has to be treated, and to do this effectively it is necessary to have efficient bacteriological facilities for following up the patients. It is suggested that such facilities are better used to prevent the attacks of acute pyelonephritis. Whatever the result of these deliberations there is no doubt that pregnant women who are known to suffer from a pre-existing renal disease should always have their urine cultured

Curative The treatment of acute pyelonephritis has been discussed on p 286 The liability for the urine to become reinfected is particularly great in pregnancy (80 per cent within six months), and treatment with antibiotics should be continued until delivery and for one month thereafter Very occasionally antibiotic treatment is unavailing, the patient's condition deteriorates rapidly and pregnancy has to be terminated

Prognosis

The ultimate prognosis following acute pyelonephritis of pregnancy is not known Intravenous pyelograms performed after delivery will occasionally show the presence of some structural abnormality, including scarring and clubbing of calyces There is now little doubt, however, that most if not all these abnormalities precede the acute attack of pyelonephritis and are more often precipitating factors rather than the results of the acute attack It is probable that most of the claims that acute pyelonephritis of pregnancy causes extensive renal damage, followed eventually by chronic renal failure, hypertension and death have been based on patients with childhood pyelonephritis (p 292) who happen to have had acute pyelonephritis during pregnancy The prognosis in such women is likely to be very different from those whose kidneys show no radiological abnormality

Geographical Differences

It is interesting to note that the incidence of radiological abnormalities of the kidneys in bacteruric women differs considerably from one place to another In London there does not appear to be any relation between the two whereas in Melbourne about half the women with bacteruria have some renal structural abnormality including a great many with evidence of " chronic pyelonephritis " It is becoming clear that the whole subject of renal infection in pregnancy presents *striking regional differences and that these should be kept in mind* when discussing any aspect of the subject

RENAL CHANGES IN TOXÆMIA OF PREGNANCY AND ECLAMPSIA

The term toxæmia of pregnancy is a semantic curiosity attached to an ill-defined syndrome of unknown cause, its most severe form is associated with hypertensive encephalopathic convulsions, when it is *called eclampsia* There is no convincing evidence that toxæmia of pregnancy is due primarily to a disturbance of renal function, though the kidneys are involved together with many other organs. Only the renal structural and functional disturbances are discussed here.

Pathology

The microscopical appearances have been studied by renal biopsy before and after delivery. There are two changes evident and they are both situated in the glomeruli. The one seen most frequently consists of minimal endothelial cell proliferation with widespread conspicuous swelling of the cytoplasm of both the endo- and epithelial cells of the glomerular tufts, more marked in the endothelial cells. These changes diminish the lumen of the capillaries and give the glomeruli a " solid " appearance. They disappear rapidly after delivery.

The other glomerular change is seldom found and is always in combination with the one just described. It consists of focal thickenings of the basement membrane; it appears to be less reversible than the first.

In autopsy material from multiparæ or elderly primiparæ who have died from eclampsia small crescents of proliferated capsular cells can be seen in the glomeruli.

Discussion on the Cause of the Renal Structural Changes

It is likely that the initial abnormality in toxæmia of pregnancy is ischæmia of the placenta. This may be due either to vascular disease of the uterine arteries such as that associated with pre-existing hypertension, or to some less obvious cause such as circulating placental antibodies formed by the mother. In some way that is not clear placental ischæmia then causes the release of a clot-promoting agent into the circulation which produces intravascular clotting. Fibrin and its breakdown products then accumulate on the surface endothelium of the vascular system including the glomerular capillaries where it is absorbed into the endothelial cells and causes them to swell and proliferate.

This sequence is supported by the following evidence. (1) There is both anatomical and functional evidence that the irrigation of the uterus by blood is impaired in toxæmia of pregnancy. (2) The blood of pregnant women contains an increased concentration of cryofibrinogen, and this rises considerably in toxæmia of pregnancy (and when pregnancy is complicated by infection). (3) Immuno-fluorescent studies on renal biopsies have shown that there is a striking accumulation of fibrinogen derivatives within the endothelial cells, whereas gamma globulin and complement are not demonstrable which provides strong evidence against an immunological basis for the glomerular lesion.

(4) In some instances fibrinoid deposits are found in the glomerular tufts, and in especially severe cases occlusive masses of fibrin are found in the glomerular capillaries, sometimes leading to cortical necrosis (5) Glomerular lesions similar to those observed in toxæmia of pregnancy can be produced in rabbits by inducing a slow prolonged state of intravascular coagulation

Renal Function

It is a remarkable fact that the renal blood flow in toxæmia of pregnancy is frequently within normal limits, though there is wide variation both above and below normal The commonest abnormality is a fall in glomerular filtration rate it may fall to 50 ml /min without a decrease in renal blood flow *It is possible that the depression in glomerular filtration rate is due to the cytoplasmic swelling of the cells lining the glomerular tufts The fall in filtration rate often bears no* relation to the clinical severity of the toxæmia After delivery there is a sudden rise in filtration rate and for a short time it may reach 250 ml / min , there is an accompanying diuresis and urine volumes up to 550 ml an hour have been described

In severe eclampsia there is a generalised peripheral vasoconstriction and as in all clinical conditions associated with generalised vasoconstriction it is particularly marked in the kidney Renal ischæmia may be sufficiently prolonged and extensive to cause acute tubular necrosis and acute renal failure

The œdema and oliguria of toxæmia in pregnancy have not been explained satisfactorily The urinary excretion of ketogenic steroids and aldosterone is either normal or decreased Measurement of total exchangeable sodium has given conflicting results There is no agreement whether the œdema is due to sodium retention or to a shift of sodium

Hypertension is a constant accompaniment of toxæmia of pregnancy It has repeatedly been shown that it can be present without any detectable change in renal blood flow It would seem, therefore, that the hypertension of toxæmia of pregnancy is not caused by an overall change in renal circulation, but it may still be related to some intrarenal circulatory disturbance

Proteinuria nearly always occurs and presumably results from the structural changes in the glomeruli

Clinical Features

Toxæmia of pregnancy *occurs most frequently in primigravidæ* and in women who have a persistent rise in blood pressure before the start *of pregnancy*

The disease is characterised by hypertension, œdema and proteinuria. It is not an acute nephritic syndrome, for the jugular venous and right auricular pressures are usually normal, i.e. pulmonary venous congestion does not occur, except very occasionally in the terminal phase of eclampsia. Nor does it fit within the definition of a nephrotic syndrome, for again, with the exception of very severe cases, the plasma protein concentrations are relatively normal or are altered to only a minor extent, and proteinuria is never greater than 5 g./ 24 hours.

The onset takes place after the first twenty weeks of pregnancy and is most common in the last six. It can be predicted to a certain extent, for it occurs in those women who have put on weight too rapidly, though 50 per cent of these will have a normal pregnancy. The first symptoms may be headache or dizziness due to the rise in blood pressure, or there may be œdema, or the patient may have symptomless proteinuria. The upper normal limit of the blood pressure in pregnancy is about 120/80 and a rise above this level may precede the onset of œdema, or proteinuria, by many weeks. As the blood pressure rises there may be visual disturbances from vascular changes in the retinæ; hypertensive encephalopathy is nearly always preceded by intense, boring frontal headache. In some cases there may be epigastric pain, sometimes of great severity. From the initial symptom to the first convulsion the syndrome may be telescoped into a matter of hours; fortunately the development of symptoms is usually slower. There is always some degree of oliguria. With the convulsions there may be temporary anuria, and very occasionally acute renal failure develops. Unless there is acute renal failure the specific gravity of the urine during a period of oliguria is high.

After delivery the symptoms and signs usually subside rapidly, though in exceptional cases the most prominent features of the disease may occur in the first two or three days of the puerperium.

Relation between Clinical and Structural Features

Excluding those exceptional cases of eclampsia who develop acute renal failure from tubular necrosis or widespread arteriolonecrotic lesions, there seems to be little relation between the severity of the pathological lesions and the clinical picture; the changes in mild toxæmia and in eclampsia may be identical. There is a good correlation however, between the histological changes and the plasma concentration of uric acid. The rise in uric acid is due to a simultaneous rise in plasma lactic acid which accelerates tubular reabsorption of uric acid and thus diminishes uric acid excretion (p. 79). The cause of the rise in lactic acid is obscure: it is probably related to ischæmia of the placenta.

Differential Diagnosis

It is essential to exclude contamination of the urine by protein from vaginal discharge

If persistent proteinuria is found before the twentieth week it is most unlikely to be due to toxæmia of pregnancy At this time the most common causes of proteinuria are orthostatic proteinuria and chronic renal disease Excluding acute pyelonephritis, which is not difficult to diagnose, other acute renal diseases are very rare during pregnancy (p 339) Other causes of proteinuria include cardiac failure, severe anæmia and renal tuberculosis

If the urine is not examined before the twentieth week, and proteinuria is found subsequently all these causes of proteinuria must be considered as well as the probability of toxæmia of pregnancy

Not many patients with toxæmia of pregnancy have a urinary infection. But a large proportion of women with radiological evidence of childhood pyelonephritis develop toxæmia when pregnant

Prognosis

The immediate prognosis of toxæmia of pregnancy is excellent, unless there are fits, the mortality of eclampsia varies between 10–40 per cent, one of the causes of death being acute renal failure

The ultimate prognosis is difficult to assess Following toxæmia of pregnancy some women develop a persistent rise in blood pressure and their prognosis is then that of hypertension, including its effects on the kidney This would seem to indicate that toxæmia of pregnancy may cause persistent hypertension Nevertheless statistical evidence shows that the incidence of hypertensive vascular disease in women is the same whether or not they have borne children The conclusion, which is generally accepted, is that persistent hypertension following toxæmia of pregnancy only develops in women who were inevitably bound to have a rise in blood pressure later, and that the toxæmia of pregnancy has only accelerated its onset The situation is complicated further by the fact that in a few patients it has been demonstrated that persistent hypertension following toxæmia has been due to renal artery stenosis It is clear that persistent hypertension following toxæmia should always be thoroughly investigated

The incidence of persistent hypertension following toxæmia of pregnancy varies considerably in different series One report states that it is 20 per cent following eclampsia and 40 per cent following non-convulsive toxæmia This paradox is attributed to (1) the fact that non-convulsive toxæmia usually lasts longer than eclampsia, for there is a positive correlation between the duration of toxæmia and residual hypertension, and (2) the diagnosis of non-convulsive toxæmia is often uncertain and may include some patients who had hypertension before pregnancy who may, therefore, only have essential hypertension.

There is no published evidence that toxæmia of pregnancy gives rise to chronic renal disease other than that which may accompany the subsequent hypertension. Occasionally, however, a patient whose urine is known to have been protein-free before pregnancy develops persistent proteinuria without hypertension after pregnancy, having had toxæmia during pregnancy. Biopsy of such patients several years later shows peristing structural alterations in the glomeruli, particularly of the basement membrane. The prognosis in these patients is not known.

When a woman has had non-convulsive toxæmia of pregnancy in her first pregnancy the incidence of toxæmia in the second pregnancy is about 30 per cent. If a multiparous woman has had non-convulsive toxæmia the incidence of a recurrence of toxæmia with a subsequent pregnancy is about 60 per cent. These figures are slightly less following eclampsia, and greater in women with persistent hypertension between pregnancies.

Treatment

Toxæmia of pregnancy is unlikely to occur in women who avoid putting on more than 5 lb. in any one month or more than 10 lb. in the last three months. If these limits are exceeded a low-salt, high-protein, low-calorie diet is given with vitamin and mineral supplements until the position has been readjusted.

Once toxæmia of pregnancy has declared itself the best treatment is bed rest, sedatives and a similar diet to that described above, except that it should be as salt-free as possible. Infection should be looked for and treated vigorously. If the blood pressure continues to rise, with increasing proteinuria and the development of retinal changes, hypotensive drugs or spinal anæsthesia can be tried while the effect of the salt restriction and bed rest are given time to take effect; if there is a continued and uncontrollable deterioration, pregnancy must be terminated. The treatment of hypertensive encephalopathy consists in sedation, lowering the blood pressure, and termination of pregnancy.

It is important to keep in mind that acute renal failure may develop, in order that its treatment may not be delayed.

ACUTE RENAL FAILURE DURING PREGNANCY

Acute renal failure either occurs early in pregnancy when it is usually due to criminal abortion, or it occurs at the end of pregnancy, when it is a complication of pre eclamptic toxæmia, accidental hæmorrhage or post partum hæmorrhage

Acute Renal Failure Complicating Abortion

The cause is loss of blood, reduction in blood volume and intense renal ischæmia (p 92) The frequency with which this eventually causes renal failure in abortions is presumably related to the prolonged period of renal ischæmia which occurs before qualified medical help is sought Most of these patients suffer from pelvic sepsis, often with *Cl welchii* or *Staph aureus* Death occurs in approximately half the cases and is nearly always due to sepsis, not to renal failure

Acute Renal Failure in Late Pregnancy

Again the cause of the renal lesion is renal ischæmia resulting from hæmorrhage It is possible that in addition there may be a direct nervous vasoconstricting stimulus from the uterus to the kidneys (p 93) And in some cases when it is associated with toxæmia, to the deposition of fibrin within the glomerular capillaries

Acute tubular necrosis is much more common with accidental hæmorrhage (approximately 12 per cent of all cases) than following postpartum hæmorrhage, and yet the blood pressure remains unchanged or rises in the former and tends to fall in the latter The most likely explanation is that the compensatory renal vasoconstriction which accompanies the reduction in circulating blood volume following postpartum hæmorrhage is not so great or so prolonged as in accidental hæmorrhage

Occasionally eclampsia may cause acute renal failure because of widespread arteriolonecrotic lesions, similar in all respects to those found in malignant hypertension

Death occurs in an uncertain number and is usually due to irreversible renal failure associated with extensive cortical necrosis

Pathology

The ischæmic tubular necrosis may be focal as described on p 147, or may be so extensive that the entire cortex is involved, when the condition is known as " cortical necrosis " In the more severe and extensive lesions the arteries are also necrosed and contain thrombi

Clinical Features, Course and Treatment

Diagnosis is often delayed because the focus of concern is initially on the poor circulatory state of the patient The clinical features and treatment of acute renal failure have been described on p 147

One of the aims of treatment is to prevent the development of acute renal failure. In eclampsia the use of hypotensive drugs or caudal anæsthesia to produce a widespread vasodilatation will not only lower the blood pressure and control the convulsions, but will diminish the renal vasoconstriction and prevent tubular necrosis. Often the quantity of blood that has been lost is underestimated for the clinical signs of blood loss may be trivial. Quick, repeated, bedside blood volume measurements with small computerised machines can be very helpful. If uterine stretch is considered to be an important factor in the acute renal failure of accidental hæmorrhage it would seem reasonable to rupture the membranes as soon as the diagnosis of accidental hæmorrhage is made.

The importance of infection in acute renal failure following abortion is such that all these patients should be given large doses of penicillin and ampicillin on admission (i.e. immediately after a high vaginal swab has been obtained for culture). Neither pelvic infection early in pregnancy nor an enlarged uterus late in pregnancy is a contra-indication to peritoneal dialysis provided the catheter is inserted high in the abdomen.

PREGNANCY IN RELATION TO PRE-EXISTING CHRONIC RENAL DISEASE

Opinions vary. Addis, after a long experience, stated that " There is no instance in which we can be sure that the renal lesion interfered with pregnancy. There is no evidence that any of them have been harmed by pregnancy." Other authors are less sanguine. The opinions given below are those most widely held; there is little quantitative information available.

The Effect of Chronic Renal Disease on Pregnancy

The outstanding fact is that women with chronic renal disease (particularly glomerular nephritis) are usually sterile. Those who do become pregnant are extremely liable to abort at the third to the fifth month of pregnancy, or to develop accidental hæmorrhage later. Toxæmia of pregnancy and eclampsia are uncommon complications. Some women have a normal pregnancy, though the fœtus is apt to be small. It is probable that the prognosis depends on the height of the blood pressure before conception, as well as the extent of the renal failure. Because of the dangers of accidental hæmorrhage it is usual to terminate pregnancy, if the fœtus is sufficiently large, at about the thirty-third week.

The Effect of Pregnancy on Chronic Renal Disease

With glomerular nephritis the issue is relatively clear cut Either there is a sudden deterioration in renal function, with increased proteinuria and a rise in blood pressure before the twentieth week or pregnancy causes no harm When there is an exacerbation of the renal disease some permanent additional impairment of function remains thereafter The proteinuria of diabetic nephropathy often increases during pregnancy but improves again after delivery

With other renal diseases, such as chronic pyelonephritis or polycystic disease, the prognosis depends more directly and less mysteriously on whether or not renal infections are allowed to develop

It is nearly always impossible to predict the probable course of events If a woman with chronic renal disease is anxious to have a child and is aware of the risks involved, it is reasonable that she should try and become pregnant only if her blood pressure is normal and renal function is not less than 50 per cent of normal Once pregnancy has begun, renal infections should be prevented (p 286), and renal function, urine deposit, the extent of the proteinuria and the height of the blood pressure carefully watched Pregnancy is discontinued at once if there is evidence of an exacerbation of renal disease

Women with chronic renal disease and hypertension and/or moderately well advanced renal failure (blood urea 100 mg /100 ml or more) should not become pregnant, for any further deterioration in renal function may be crippling Pregnancies should be terminated if they occur

Unilateral Kidney

When there is only one kidney pregnancy should not be attempted until the functional and structural state of the kidney has been examined, it should be remembered that a nephrectomy is often performed for a renal disease which may be bilateral

Ectopic Kidney

If both kidneys are ectopic the fœtus should be delivered by Cæsarean section If there is only one ectopic kidney it is worth attempting a normal birth, but if there are likely to be any complications such as a breech presentation, it is best to do a Cæsarean section

THE INCIDENCE OF OTHER RENAL DISEASES IN PREGNANCY

Excluding renal infections, the onset of a new renal disease during pregnancy is very rare Acute glomerular nephritis is the most common There is no difficulty in diagnosis if attention is paid to the jugular venous pressure and the urinary deposit. The sudden onset of pulmonary congestion and rise in blood pressure excludes other causes of proteinuria and œdema. If the acute phase of the disease is safely negotiated pregnancy may continue normally with no permanent deterioration of renal function evident.

Very occasionally nephrotic glomerular nephritis may develop for the first time during pregnancy. The massive proteinuria, the normal blood pressure and jugular venous pressure distinguish the diagnosis. Such patients have occasionally been successfully treated with cortisone or prednisone and had a normal pregnancy.

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26

THROMBOSIS OF THE RENAL ARTERY AND VEIN

Renal Artery Thrombosis

AN uncommon condition which occurs particularly in elderly patients with advanced atheromatous vascular disease who have previously suffered from cerebral or coronary thrombosis, or peripheral arterial disease.

Pathology

The thrombus is either in the main renal artery or it may be confined to one or two of its branches. With occlusion of the main vessel the kidney becomes smaller, pale and bloodless. If, however, some of the renal veins become thrombosed at the same time there will be localised areas of congestive and interstitial œdema.

Clinical Features

In contrast to renal vein thrombosis the outstanding presenting symptom is severe pain. The patient usually presents as an acute emergency, either abdominal, if the pain is in the flank or hypochondrium, or cardiac or respiratory if it radiates to the lower chest. Nausea and vomiting are common.

There is acute tenderness in the renal angle and flank, but there may be no rigidity. Hæmaturia sometimes occurs, presumably if there is a concomitant thrombosis of the renal veins.

A straight X-ray of the abdomen often shows a calcified abdominal aorta and an I.V.P. confirms that the condition is renal, for no dye is secreted on the side of the pain and tenderness. At cystoscopy no urine is seen emerging from the ureteric orifice, but a retrograde pyelogram shows a normal pelvis and calyces. Subsequently the affected kidney becomes smaller while the normal kidney becomes larger. An aortogram confirms that there is no blood flow into the renal artery of the affected kidney.

Prognosis

The immediate prognosis is more concerned with the functional integrity of the other organs, e.g. whether cardiac failure was present before the renal arterial thrombosis occurred.

Occasionally when the patient survives, the artery recanalises and there is a sudden onset of severe malignant hypertension in the next few weeks due to renal artery stenosis (p 116)

Treatment

The patient's general condition usually precludes any measures other than those of anticoagulant therapy, rest and symptomatic treatment

If the thrombosis occurs in a young subject, because of a localised structural anomaly of the renal artery, the kidney should be removed, particularly if the blood pressure begins to rise.

Renal Vein Thrombosis

Thrombosis of the renal veins is an extremely rare condition The thrombus may either originate in the inferior vena cava and spread laterally into the renal veins, or it may begin in the smaller veins within the parenchyma of a diseased kidney and spread medially

Pathology

The usual biopsy specimen obtained several weeks or months after the onset of the thrombosis, usually shows merely a few insignificant and unspecific changes, and is only of value in a negative sense One renal biopsy, performed a few days after the onset, showed extensive interstitial œdema

At autopsy the diagnostic feature is the finding of a thrombus in the renal vein with, in long standing cases the presence of large collateral venous channels between the capsule of the kidney and the surrounding tissues Microscopically the glomeruli appear normal and the tubules are unchanged unless there has been much proteinuria, when the tubule cells will contain lipoid material and collections of an eosin staining substance, though in some long standing cases there is considerable tubular atrophy and tubular separation

Inferior vena caval thrombosis may be spontaneous, or may be due to invasion by neoplasm, or to external compression The most common renal disease to give rise to intrarenal venous thrombosis in adults is renal amyloidosis, it occasionally occurs with chronic pyelonephritis In infants renal vein thrombosis is often associated with acute pyelonephritis

Clinical Features

These depend on the rapidity of the thrombotic process, whether it is unilateral or bilateral and if it is secondary to inferior vena caval thrombosis

When the thrombosis is rapid, bilateral, and has spread from the inferior vena cava, there is sudden back pain extending into the flanks with oliguria, proteinuria and hæmaturia leading to renal failure with œdema of the lower limbs and the anterior abdominal wall. Death may occur rapidly from acute renal failure.

If the thrombosis is bilateral but the inferior vena cava is unobstructed there is no œdema of the lower limbs. In adults this is usually due to renal disease. In infants acute bilateral renal vein thrombosis often follows acute gastro-enteritis, when the thrombosis is presumably caused by intense renal ischæmia in otherwise normal kidneys; or it may be associated with acute pyelonephritis; there is usually sepsis elsewhere, and the sudden onset of flank tenderness and pyuria with a swinging fever may suggest the diagnosis. Acute renal failure and death are the usual outcome.

Occasionally, however, the onset of bilateral renal vein thrombosis in adults (whether or not it is associated with inferior vena caval thrombosis) is less acute and may pass unnoticed, or the initial disturbance is followed by a large measure of recovery. Some of these cases may subsequently develop a nephrotic syndrome and, unless it is accompanied by evidence of inferior vena caval thrombosis with large collateral channels on the anterior abdominal wall, the thrombosis of the renal veins is unsuspected. In a few patients all evidence of renal disturbance may disappear except for the continued presence of a mild proteinuria. It is questionable whether *unilateral* renal vein thrombosis can give rise to *bilateral* histological lesions of immunological renal disease, together with a nephrotic syndrome, or whether such histological changes always precede the renal vein thrombosis; the latter seems the more likely.

The clinical course probably depends on the ability to recanalise the thrombus and establish a collateral venous circulation.

Diagnosis

The sudden onset of oliguria, proteinuria, raised blood urea, and severe œdema confined to the lower limbs, without evidence of cardiac failure or hypoproteinæmia, should make one suspect the condition. Collateral venous channels on the anterior abdominal wall do not appear until several weeks or months after the onset, but once they are evident they greatly simplify the diagnosis in those cases of inferior vena caval and renal vein thrombosis who have survived the acute phase.

Treatment

If the onset is recognised in adults it is reasonable to give anticoagulants; otherwise treatment is symptomatic.

In infants with pyelonephritis a nephrectomy may prevent the spread of the septic thrombus into the inferior vena cava and across to the other kidney.

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27

HÆMOGLOBINURIA AND MYOGLOBINURIA

Hæmoglobinuria is the term used for the appearance of free hæmoglobin in the urine. It follows hæmolysis of red cells, either in the blood stream or in the urine.

Free hæmoglobin is about the biggest naturally occurring molecule that can pass freely through the normal glomerular membrane (mol. wt. 68,000). Hæmoglobin in plasma is normally bound to protein and is present in a concentration of about 5 mg./100 ml. In a normal individual there is sufficient hæmoglobin binding protein (haptoglobins) to bind concentrations of hæmoglobin up to 100–125 mg./100 ml. The bound hæmoglobin does not pass through the glomerulus. The unbound or free form of hæmoglobin passes readily through the glomerulus, some is reabsorbed in the proximal tubule, and the rest promptly appears in the urine. Tubular reabsorption of hæmoglobin is always associated with hæmosiderinuria, for as the hæmoglobin is processed through the tubule cell some of the molecule is converted into hæmosiderin and excreted into the urine. Hæmosiderinuria will therefore be present when there is free hæmoglobin in the plasma whether or not there is hæmoglobinuria.

Myohæmoglobin is a muscle protein with a molecular weight of 17,000; it permeates freely through the glomerulus, and little seems to be reabsorbed by the tubule; it first appears in the urine when the plasma concentration is about 10 mg./100 ml., and its rate of excretion is extremely rapid. For this reason it is rarely detected in the blood.

Methods of Identification

Hæmoglobin and Myohæmoglobin

These can be identified in solution, either spectroscopically or by the colour that is produced when they react with tolidine. A few milligrammes of purified tolidine hydrochloride are dissolved in 5 ml. of glacial acetic acid; 1 ml. of this solution and 1 ml. of freshly prepared hydrogen peroxide are added to 2 ml. of urine. The presence of hæmoglobin or myohæmoglobin in considerable amounts will turn the urine blue; a lesser amount will only produce a green colour. If a simultaneous sample of blood is obtained and centrifuged and the *supernatant plasma is pink the material in the urine is hæmoglobin* whereas if the plasma is not pink the urine contains myoglobin

Hæmosiderin

In contrast to hæmoglobin and myohæmoglobin which are in solution, hæmosiderin in the urine is present in particulate form, either *in disintegrating tubule cells or as amorphous debris* The test for hæmosiderinuria consists, therefore, in using the Prussian blue reaction to stain the urine sediment About 20 ml of urine is centrifuged and *all but 1 ml. of the supernatant fluid is discarded 1 ml of 5 per cent* hydrochloric acid and 0 5 ml of a 10 per cent aqueous solution of potassium ferrocyanide are than added to the 1 ml of urine in which *the deposit has been resuspended A drop is then examined under the* microscope, when hæmosiderin will appear as deep blue flecks lying free or within the tubule cells and casts

Renal Changes Associated with Hæmoglobinuria

Changes Associated with Acute Hæmoglobinuria

Large amounts of hæmoglobin have been given experimentally both to normal man and animals There are either no adverse effects on the kidneys or a transient reduction in glomerular filtration rate Renal blood flow is unchanged though PAH clearance falls There is also a transient fall in urine flow

Under clinical conditions, however, hæmoglobinuria is occasionally associated with acute renal failure It has also been observed that if hæmoglobin is given to animals that are oligæmic or dehydrated, tubular necrosis may occur with numerous hæmcasts in the distal and collecting tubules

It is probable, therefore, that several closely connected factors are responsible for the renal failure that follows clinical hæmoglobinuria Pre existing oligæmia or dehydration are usually present and have caused renal vasoconstriction with an acute reduction in glomerular filtration rate before the onset of hæmoglobinuria, and have also resulted in a high concentration of circulating anti diuretic hormone (ADH) This combination causes a maximal reabsorption of water from the glomerular filtrate so that the hæmoglobin in the tubule lumen is highly concentrated, it then precipitates and causes obstruction of the nephron

The pathological changes have been described in Section 12 There are focal areas of tubular necrosis, hæmcasts and occasional collections of interstitial inflammatory cells Large amounts of hæmosiderin may be found in the tubule cells

Changes Associated with Chronic Hæmoglobinuria

There are two functional changes; proteinuria and persistent hæmosiderinuria. Structurally the accumulation of hæmosiderin in the tubule cell appears to be the only change which is specifically due to the hæmoglobinuria. In addition, hæmoglobin appears in the urine at lower plasma concentrations of hæmoglobin than in acute hæmoglobinæmia. Following several hæmoglobinuric crises hæmoglobin may appear in the urine when the plasma concentration is only 25 mg./100 ml. This is because the normal rate of production of hæmoglobin binding protein is insufficient to keep up with the large quantities of hæmoglobin that are liberated.

Ætiology

The following conditions may cause hæmoglobinuria:

FOLLOWING INTRAVASCULAR HÆMOLYSIS:

1. Exercise: (*a*) Very strenuous exercise.
   (*b*) March hæmoglobinuria.
2. Mismatched transfusion.
3. Paroxysmal nocturnal hæmoglobinuria.
4. Blackwater fever.
5. Hypotonicity of the plasma (prostatic surgery).
6. Thermal and chemical injuries.
7. Paroxysmal cold hæmoglobinuria.

Other common causes of hæmolysis, such as congenital spherocytosis or acquired hæmolytic anæmia due to abnormal serum antibodies, rarely cause hæmoglobinuria, for the rate of destruction is slower and the site of hæmolysis is in the reticulo-endothelial system.

FOLLOWING HÆMOLYSIS IN THE URINE:

1. Any cause of hæmaturia when the specific gravity of the urine is below 1·007.
2. Renal infarction.

HÆMOGLOBINURIA FOLLOWING INTRAVASCULAR HÆMOLYSIS

Exercise

Any normal person who undergoes sufficiently severe and prolonged strenuous exercise will have hæmoglobinuria and proteinuria. This has been shown particularly in marathon runners. It is a benign complication of strenuous exercise, with no late sequelæ.

There are in addition certain individuals who develop considerable hæmoglobinuria and proteinuria upon performing any moderate exercise, e g a brisk walk, or a short run The cause of the phenomenon is unexplained. It is due to intravascular hæmolysis which only occurs in the upright posture, vigorous exercise taken in the horizontal posture does not produce hæmoglobinuria It is a benign condition sometimes associated with increased amino-aciduria, and is known as March hæmoglobinuria There is no treatment There are spontaneous fluctuations in the tendency to hæmolyse, when relapses occur physical exercise should be curtailed If relapses are frequent they can sometimes be lessened by putting " sorbo " rubber insoles into the shoes, the implication being that hæmolysis may result from damage to red cells in the soles of the feet

Mismatched Transfusion

In temperate climates, this is the most common cause of hæmoglobinuria to be followed by acute renal failure Plasma concentrations of hæmoglobin may rise to 1,000 mg /100 ml or more, there is fever, shivering, severe pains in the back, hypotension and discoloured urine

Transfusions are most frequently given because of recent loss of blood If, when blood is being administered, the patient develops symptoms which suggest that hæmolysis is taking place, the transfusion should be stopped immediately A sample of the *patient s blood* is then centrifuged and the supernatant plasma examined by naked eye for the presence of hæmoglobin If the plasma is not pink, then hæmolysis is not the cause of the patient's symptoms and the administration of blood should be continued with a fresh bottle of blood The previous bottle may have contained some other protein which caused the patient's reaction, it may, for example, have been infected This is insufficient reason for abandoning the attempt to replace the lost blood

If, however, the plasma clearly contains hæmoglobin, then no further blood transfusions should be given It is essential nevertheless to try and overcome the renal vasoconstriction of the oligæmia, and a plasma expander such as Dextran should be given in as large amounts as possible, e.g about one to two litres If anæmia (as opposed to oligæmia) is then severe the patient should be placed in an oxygen tent, for by increasing the plasma oxygen tension there may be sufficient improvement in his general condition to influence the extent of renal damage It has been claimed that acute renal failure following mismatched transfusion can be avoided or cut short by immediate exchange transfusion Cannulæ are placed in the radial artery and cephalic vein, and the exchange begun with a litre of a plasma expander It is continued with properly cross-matched blood. The duration of the exchange is determined by the concentration of the circulating hæmoglobin in the plasma. An exchange of 5 to 8 l. can reduce the circulating concentration from about 800 mg. to 100 mg./ml. In addition to eliminating the hæmoglobin, exchange transfusion has an added advantage in that it supplies large quantities of fresh hæmoglobin binding protein, so that a high proportion of the hæmoglobin that remains is bound to protein and not filtrable.

Paroxysmal Nocturnal Hæmoglobinuria

This is a rare disease characterised by an acquired abnormality of the red cells which greatly shortens their survival. Unlike most other causes of abnormal red cell destruction the cells in paroxysmal nocturnal hæmoglobinuria are destroyed in the plasma, as opposed to the reticulo-endothelial system. This gives rise to high plasma concentrations of hæmoglobin. The hæmolytic process is particularly severe during sleep, so that the urine may be purple in the morning but a normal colour by evening. If the patient sleeps during the day the process is reversed. It has been demonstrated that the acceleration of hæmolysis that occurs during sleep is not due to any accompanying change in plasma *p*H that may occur at that time.

The disease becomes manifest usually between the ages of 20 and 40, and occurs equally in both sexes. The tendency to hæmolyse fluctuates, and during relapses hæmoglobinæmia is continuous, though hæmoglobinuria comes on in sudden sharp attacks. In addition to the discoloured urine these acute episodes are associated with headache, backache, muscular and abdominal pains. Acute hæmolytic crises are sometimes brought on by mild infections. There may be severe anæmia and there is a continuous reticulocytosis; eventually the patient develops a pale brown pigmentation. Occasionally there may be remissions of a few weeks or months when the total blood hæmoglobin concentration returns to normal, but hæmosiderinuria continues uninterruptedly. Death usually occurs from thrombosis of visceral veins including the mesenteric, splenic and renal.

The anæmia cannot be treated with transfusions of ordinary blood, for these cause an intense hæmolysis of the *patient's* red cells. This reaction is due to some substance present in the donated plasma, and can be avoided by giving red cells washed and suspended in saline.

Blackwater Fever

This complication of malignant tertian malaria usually occurs in those who have previously been treated with antimalarial drugs, particularly quinine, either prophylactically or for recurrent attacks of malaria There is a sudden and severe hæmolysis of unknown cause sometimes followed by acute renal failure

Hypotonicity of Plasma

Transurethral resections of the prostate are usually carried out with intermittent washouts of the bladder and urethra with water If much water is absorbed during this procedure there may be hæmolysis near the site of absorption where the plasma osmolality is grossly reduced there is then hæmoglobinæmia and occasionally hæmoglobinuria sometimes acute renal failure may develop

Thermal and Chemical Injuries

Patients with severe burns may develop hæmoglobinæmia and hæmoglobinuria from destruction of the red cells contained in or near the affected areas Acute renal failure occurs quite frequently and though this is mainly due to renal ischæmia from the reduced blood volume it is obvious that a superimposed hæmoglobinæmia will only make its development more likely

Arsine causes spherocytosis and acute hæmolysis Death from severe anæmia may occur a few hours later The gas is produced when certain metals and acids containing arsenic come into contact

Other chemicals which sometimes cause severe hæmolysis and hæmoglobinuria include naphthalene (moth balls) sulphonamides and mephanesin

Paroxysmal Cold Hæmoglobinuria

This condition is characterised by sudden attacks of hæmolysis which follow the cooling of a part or the whole of the body It is due to an autohæmolysin which only becomes attached to the red cells at body temperatures below normal When such red cells circulate to parts of the body with a normal temperature they are hæmolysed Severe attacks are associated with rigors fever and anæmia acute renal *failure does not occur*

The disorder occurs in congenital and acquired syphilis and sometimes follows certain acute infections such as virus pneumonia

HÆMOGLOBINURIA FOLLOWING HÆMOLYSIS IN THE URINE

If there is hæmaturia and the urine concentration falls below approximately S G 1 007 the red cells will hæmolyse and there will be free hæmoglobin in the urine This is only important as a diagnostic trap It will be recognised if the urine specific gravity is measured and the deposit examined microscopically for red cells and casts

It has been reported that acute renal *infarction may be associated* with unilateral hæmoglobinuria

MYOGLOBINURIA

Renal Changes Associated with Myoglobinuria

There is no doubt that myoglobinuria may by itself cause acute renal failure. This has been clearly demonstrated in a patient who was being extensively investigated in hospital. Myoglobinuria could be induced by exercise. Following a particularly severe bout of exercise the patient developed acute renal failure and was oliguric for 14 days. Fortunately he recovered.

Usually when acute renal failure develops in combination with myoglobinuria the cause of the failure is as obscure and complicated as in hæmoglobinuria. For instance, myoglobinæmia, myoglobinuria and acute renal failure can occur in crush injuries. But injuries are associated with acute renal failure in the absence of myoglobinuria. The importance of the myoglobinuria in the ætiology of acute renal failure following injury has always been, and is likely to remain, problematical.

The cause of the renal failure which follows myoglobinuria is not clear. Widespread tubular obstruction must be one of the factors, for casts of precipitated myoglobin can be seen in the tubular lumens.

Clinical Features

Myoglobinuria results from rapid destruction of muscle. This may follow some obvious cause such as crush injuries, high voltage shock or localised muscle necrosis due to postural pressure during coma (e.g. gas poisoning or alcoholic intoxication); it has also been described with sudden arterial occlusion and after severe convulsions. The other causes of acute muscle destruction are various biochemical disturbances which are not understood. One is said to be due to allergy to sea food, another is a variant of muscular dystrophy; and the most common is that known as idiopathic paroxysmal myoglobinuria.

Idiopathic Paroxysmal Myoglobinuria

The tendency to attacks fluctuates, but it is unusual to have more than one attack a year. They are usually precipitated by strenuous exercise. The patient wakes up complaining of severe pain and stiffness in those muscles which were involved in the exercise, and that his urine is dark brown. On examination, the affected muscles are firm, tender and exquisitely painful upon being stretched. Walking may not be possible. The urine is dark but clear. The diagnosis can be made in the ward by finding that the substance in the urine is tolidine positive, i.e. that the urine contains large quantities of either hæmoglobin or myohæmoglobin, when the plasma has a normal colour. It follows that the substance in the urine is myoglobin for if it were hæmoglobin the plasma would be pink from hæmoglobinæmia Myoglobin is never present *in the plasma in sufficient quantities to discolour it*, for as it is not bound to protein and easily filtered at the glomerulus, it is rapidly excreted.

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28

PORPHYRIA

PORPHYRIA is a rare and often familial disorder of porphyrin metabolism which results in widespread abnormalities, particularly in the skin, gastro-intestinal tract and central nervous system. Frequently there are acute exacerbations which may be associated with renal disturbances.

Pathology

Porphyrins form part of the hæmoglobin molecule. In porphyria their metabolism is disturbed, so that their concentration in the blood rises and they are excreted in increased quantities both in the urine and fæces. Several types of porphyrins are involved, but during an acute attack there is one, porphobilinogen, which is always present in large amounts.

Porphobilinogen is a colourless chromogen. Its presence, however, can sometimes be suspected on naked eye examination of the urine, for its breakdown products on standing give the urine an orange or nectarine-like colour; this is usually overlooked for it is confused with the appearance of a concentrated urine. The presence of porphobilinogen is confirmed with Ehrlich's reagent (the same which is used for detecting the presence of urobilinogen). Both urobilinogen and porphobilinogen give a red colour within 20 seconds; they are then differentiated by adding chloroform; if the red colour remains outside the chloroform the colour is due to porphobilinogen; if it goes into the chloroform the colour is due to urobilinogen.

Frequently, acute porphyria is associated with an increased excretion of other porphyrins which may turn the urine dark purple.

At autopsy large amounts of porphyrins can be identified in the tubule cells. These probably account for the disturbance of tubular function.

Clinical Features of Acute Porphyria

Acute porphyria is often provoked by the administration of barbiturates. Its main clinical features are abdominal pain, constipation, tachycardia, hypertension and peripheral neuritis. Later, there may be coma, generalised flaccid paralysis and jaundice. In addition the most advanced cases develop an uncontrolled diuresis with extensive loss of sodium, potassium chloride and water which may cause circulatory collapse and death Acute intermittent porphyria is one cause of 'inappropriate secretion of antidiuretic hormone

Treatment

Prophylactic It is imperative that barbiturates (and possibly also sulphonamides and griseofulvin) should not be given to patients who suffer from porphyria To make sure of this the patient should be given a card on which it is clearly stated that she is suffering from porphyria and that these drugs particularly barbiturates must not be administered however anxious and mentally disturbed the patient may appear

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29

THE KIDNEY, GOUT, AND URIC ACID

ABNORMALITIES of uric acid metabolism associated with a rise in plasma uric acid can cause chronic or acute renal failure. On the other hand abnormalities in renal function can cause a rise or fall in plasma uric acid.

Structural Changes Associated with Hyperuricæmia

Chronic hyperuricæmia can cause chronic renal failure. The following changes are seen :

(*a*) Very occasionally there is an easily demonstrable deposition of urates within the renal parenchyma.
(*b*) Interstitial nephritis.
(*c*) Nephrosclerosis.
(*d*) Histological changes indistinguishable from those found in persistent glomerular nephritis.
(*e*) Uric acid stones.

Urates are found in the interstitial spaces. They cause necrosis of the tubules in the immediate vicinity of the deposits, and are surrounded by focal concentrations of inflammatory cells. Very rarely the deposits can become sufficiently large to be macroscopically recognisable tophi, particularly in the tip of the pyramids, whether or not urates are seen. The predominant histological abnormality is one of interstitial nephritis (usually called " chronic pyelonephritis," (p. 275). The vascular lesions are those sclerotic changes found in chronic hypertensive vascular disease, but hypertension is *not* essential for their presence. The finding of lesions identical to those found in persistent glomerular nephritis is unexplained. Uric acid stones contribute to the destruction of the kidneys by causing obstruction and precipitating infection.

Acute hyperuricæmia can cause acute renal failure. This is due to precipitation of urates in the lumen of the tubules, the calyces and ureters and only occurs with extremely high plasma concentrations of uric acid.

The Effect of Hyperuricæmia on Renal Function

In man, a brief intravenous infusion of urates sufficient to cause a transient rise of plasma uric acid can cause a reversible depression of glomerular filtration

A persistent rise in plasma uric acid is associated with a gradual retention of uric acid, and the deposition of uric acid in the tissues This causes a gradual deterioration of renal function which may take 10 to 20 years to become important The number of patients with "gout" who die of renal failure is uncertain It is probably around 10 to 20 per cent

A less prolonged persistent rise in plasma uric acid occurs in leukæmia, polycythæmia, congenital hæmolytic anæmia, myelomatosis and lymphosarcoma when it is due to the high turnover of cells containing large nuclei The patient usually succumbs before the rise in plasma uric acid causes any detectable impairment in renal function Occasionally, however, acute renal failure may be precipitated by treatment This follows either the administration of cytotoxic drugs or the beginning of radiotherapy There is then an enormous rise in plasma uric acid (e g up to 50 mg /100 ml) because of the widespread destruction of cells, the large quantities of filtered uric acid precipitate in the tubules causing acute obstruction Very rarely a previously healthy person, not on any treatment, may present with a rapid onset of renal failure due to a spontaneous high plasma uric acid occurring at the onset of leukæmia

The Effect of Renal Function on Plasma Uric Acid

In some patients with persistent hyperuricæmia the rise in plasma uric acid is due to a selective impairment of the kidney to excrete uric acid Initially the glomerular filtration rate is normal. Many of these patients also have an increased production of uric acid and have therefore considerable rises in their plasma concentration of uric acid This group includes those with acute arthritis (gout) and those with familial hyperuricæmia without arthritis

A similar selective impairment in the ability to excrete uric acid but without overproduction of uric acid, occurs in a number of other conditions where it may cause a mild rise in plasma uric acid It is possible that in all these conditions the kidney s inability to excrete uric acid is due to a raised plasma lactic acid which is a known inhibitor of uric acid excretion This phenomenon occurs in a proportion of patients with "essential hypertension," myxœdema, toxæmia of pregnancy, glycogen disease, ketotic conditions such as starvation and following the ingestion of alcohol

The ingestion of pyrazinamide, pempidine, mecamylamine and many diuretics, including particularly chlorothiazide and frusemide also directly inhibit tubular secretion of uric acid and may cause quite brisk rises in plasma uric acid.

The advent of renal functional deterioration in a person who already has an impaired ability to excrete uric acid will aggravate the uric acid retention and cause the rise in plasma uric acid to be more pronounced. But the development of renal failure in persons with no previous impairment in the ability to excrete uric acid does not cause a rise in plasma uric acid until the creatinine clearance is below 20 ml./min. (Fig. 29.1).

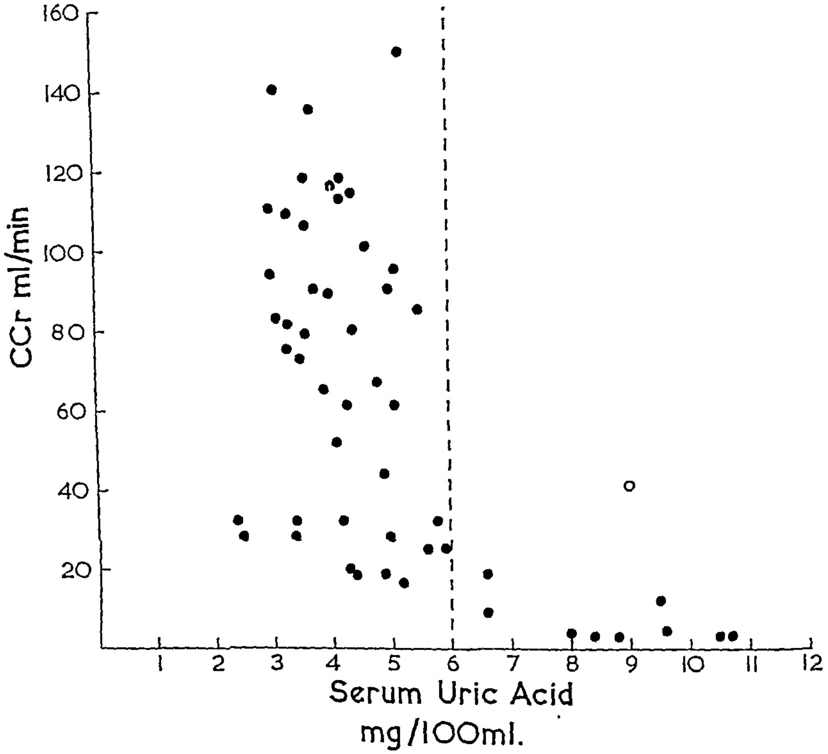

Fig. 29.1. Creatinine clearance plotted against plasma uric acid in women admitted to hospital; O = patient with a history of gouty arthritis; ● = patients with no history of gouty arthritis. (Pollard, A. C. personal communication.)

On rare occasions acute poisoning with some exogenous substance may so damage the proximal tubule's ability to reabsorb uric acid that there is a uric acid leak and a *fall* in plasma uric acid.

Clinical Features of Hyperuricæmia

If a patient is known to have a persistent rise in plasma uric acid, renal disturbances should be anticipated. The main difficulty is the variety of ways in which a patient with hyperuricæmia may present for the first time There may be the typical arthritis of gout, or multiple aches and pains which are shrugged off as "rheumatism" The young with familial hyperuricæmia may have hypertension which is first discovered either at a routine medical examination or as a sequel to toxæmia of pregnancy Sometimes asymptomatic proteinuria is the first abnormality to be noticed, or the patient first presents with acute pyelonephritis A few patients will present with uric acid stones

It is an excellent rule to measure the concentration of uric acid in the plasma of all patients suffering from proteinuria or any other renal disturbance, hypertension, arthritis or vague aches and pains The recent finding that the prognosis in essential hypertension is much worse in patients with a raised plasma uric acid makes this increasingly important

Uric acid stones may occur in any patient with hyperuricæmia due to overproduction of uric acid The stones are formed because of the increased quantity of uric acid being excreted in the urine The majority of uric acid stones, however, occur in patients with a normal plasma uric acid who are not excreting an excess amount of uric acid in the urine In these patients the stones are formed because the urine is persistently acid Whereas in a normal individual the urinary *p*H rises to 6 or higher during the day, the urinary *p*H of these patients remains below 6, or more usually below 5 5 throughout the 24 hours The cause of this functional disturbance is not clear It is associated with a moderate impairment in the ability to excrete ammonia which must contribute to the persistent acidity

The formation of stones is associated with renal colic, hæmaturia proteinuria, pyelonephritis and urinary obstruction

Treatment

Persistent hyperuricæmia can be corrected either by blocking uric acid reabsorption by the tubules or by inhibiting the production of uric acid by the liver If renal function is only moderately impaired the daily administration of probenecid will increase uric acid excretion by about a third and lower plasma uric acid As renal failure develops probenecid will become less effective It then becomes necessary to use allopurinol to inhibit xanthine oxidase activity and thus the production of uric acid from xanthine

A sudden brisk rise in plasma uric acid with uric acid precipitation in the tubules such as that which may complicate the treatment of leukæmia can be avoided by the administration of allopurinol, and preventing the patient from becoming dehydrated from vomiting

It is very important to remember that most diuretics, and severe weight reducing diets, may cause a rise in plasma uric acid. In some patients this may precipitate gout or some deterioration of renal function. In a patient with some pre-existing impairment of renal function this risk should be prevented by the administration of allopurinol as soon as the plasma uric acid begins to rise. In a patient with normal renal function the plasma uric acid can be controlled if necessary with probenecid.

Uric acid stones associated with a persistently acid urine are best treated with an increased intake of fluid and 50–100 mEq. of sodium bicarbonate per day. In elderly subjects it is important to avoid precipitating pulmonary congestion. They can be given acetazoleamide in the evening; this will increase sodium excretion and keep the urine alkaline during the night.

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30

RENAL DISTURBANCES IN MYELOMATOSIS

THIS disease is characterised by focal neoplastic proliferations of cells of the plasma cell series.

Pathology

Multiple myelomatosis is associated with a variety of renal lesions, including renal infection from myelomatous tumours compressing the spinal cord, or small collections of neoplastic myeloma cells within the renal parenchyma; in addition renal amyloidosis occurs in 5–15 per cent of all cases.

Many patients with myelomatosis, however, who die of renal failure show none of these changes; instead they develop the following structural disturbances. The most characteristic is the presence in the collecting tubules of wide and dense laminated casts. Often these are surrounded by a ring of disintegrated tubular cells, the whole complex lying within a collecting tubule whose cells appear normal. In addition there is extensive tubular atrophy, but the glomeruli remain relatively unchanged. There may also be multiple focal deposits of calcium in the casts, the tubule cells and the interstitial spaces. The appearances suggest that much of the renal functional impairment is due to blocking of the collecting tubules.

Clinical Features

In the early stages, though proteinuria and mild renal functional impairment may be present, the main clinical features which usually predominate are unrelated to the kidney. The renal complications of myelomatosis are due to (*a*) abnormal protein metabolism, (*b*) hypercalcæmia, (*c*) hyperuricæmia and (*d*) amyloidosis. Sometimes a patient with myelomatosis will first present with a nephrotic syndrome, in the absence of amyloidosis.

Disturbances of Protein Metabolism. The increased number of plasma cells is responsible for an increased production of " complete " immunoglobulins; these consist of the conjunction of a long and a short polypeptide chain. In addition, in about 50 per cent of patients with myelomatosis the production of the short polypeptide chains exceeds that of the long chains. The " complete " proteins have a molecular weight of about 160,000 and cannot pass through the glomerular filter, they are therefore found in high concentrations in the plasma but only small amounts appear in the urine The short chains, however, have a molecular weight of about 22,000 They easily pass through the glomerular filtrate and appear in high concentrations in the urine (Bence-Jones' proteinuria), but the plasma only contains relatively small amounts, unless the patient is in advanced renal failure It is the precipitation of this small molecular weight protein in the collecting ducts which often causes renal failure in myelomatosis This precipitation is sometimes induced acutely by the preliminary period of dehydration which precedes an intravenous pyelogram The proteinuria of myelomatosis nearly always contains albumin whether or not Bence-Jones' protein is also present Occasionally, however Bence-Jones' protein is the only protein present, it is important to remember that Bence-Jones' protein cannot be detected with Albustix The most accurate way to detect the presence of Bence Jones' protein is to examine the urine electrophoretically It can also be identified by warming the urine; the protein at first comes out of solution and appears as a white precipitate, but as the urine becomes warmer the precipitate redissolves and the urine becomes clear If, however, other proteins are present, the persistent precipitate which they form on heating obscures the presence of Bence-Jones' protein To establish the presence of Bence-Jones' protein when other proteins are present it is therefore necessary to filter the urine immediately after it has been brought to the boil The precipitated albumin and globulins will then be separated from the Bence-Jones' protein which remains in the clear filtrate This filtrate is observed as it cools and Bence-Jones' protein will appear when the temperature falls to 70° C It is important that the warmed urine should not be allowed to cool before it has passed through the filter, for otherwise the Bence Jones' protein is precipitated on the wrong side of the filter and does not appear in the filtrate To keep the urine warm it is best to filter small amounts at a time, to reheat the urine at frequent intervals, and to place the filter paper upon a warm funnel It is characteristic of multiple myelomatosis that if Bence Jones' protein is present, it appears in large quantities, Bence-Jones' proteinuria is sometimes found in other conditions but only in small amounts

Renal failure can also be caused by the hypercalcæmia which sometimes accompanies the massive bone resorption induced by the lesions in the bone marrow In these lesions there is also a high turnover of nucleoproteins and therefore an increased production of uric acid This may cause a sufficient rise in plasma uric acid to be responsible for a rapid deterioration of renal function (p 356) Amyloidosis occurs in 10 per cent of patients with myelomatosis and may also contribute to the renal functional impairment. It is most often seen in patients with Bence-Jones' protein.

Treatment

Death is frequently due to renal failure. Often this is precipitated by dehydration and the consequent precipitation of protein in the tubules. The patient should therefore be encouraged to drink large volumes of fluids. When the daily excretion of Bence-Jones' protein is high the fluid intake should amount to about 4 litres a day. The rate of excretion of Bence-Jones' protein can sometimes be controlled by the administration of Melphelan 2–5 mg./day. Hypercalcæmia can sometimes be controlled in the same way, or with prednisone. Hyperuricæmia can be avoided or controlled by the administration of Allopurinol (p. 359).

In order to try to prevent renal failure in myelomatosis therefore, it is imperative to measure the rate of Bence-Jones' protein excretion, and the plasma concentrations of calcium and uric acid at frequent intervals.

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31

RENAL AMYLOIDOSIS

AMYLOID is an eosinophilic substance which appears structureless on light microscopy, it may be distributed throughout all the organs of the body Its deposition is possibly related to an abnormality of the reticulo-endothelial system In experimentally produced amyloidosis there is first a proliferation of reticulum cells which when they degenerate leave behind a deposit of amyloid There may be some connection between amyloidosis and myelomatosis, for (a) amyloid deposits contain immunoglobulins, (b) the bone marrow of patients with amyloidosis often contains an excess number of plasma cells, and (c) 10 per cent of patients with myelomatosis develop amyloidosis

Pathology

The kidneys are usually smooth, resilient and enlarged The cut surface shows that both the cortex and medulla are broader than normal and the demarcation between them is sharp, the glomeruli can be identified as small translucent deposists which stain dark brown upon the addition of iodine Occasionally there is considerable disorganisation, the kidneys are small and scarred and the cortex and medulla difficult to recognise

Under the microscope amyloid material is found in the walls of all vessels, including the glomerular capillaries and the peritubular venous capillaries. In a renal biopsy specimen it is characteristic that the glomeruli may appear to be almost entirely replaced by amyloid material at a time when the glomerular filtration rate may be only moderately impaired The first changes consist of a lobular stalk thickening due to amyloid deposits in the mesangium Apart from the characteristic staining reactions, the appearances are much the same as those found in post streptococcal glomerular nephritis and diabetes Electron microscopy reveals that the basement membrane is normal, the deposits of amyloid lying on either side At autopsy the glomeruli mostly consist of solid, structureless, compact masses of amyloid of about the same size as a normal glomerulus The amyloid material, which is laid in the peritubular venous capillaries, may be very thick but does not invade the tubule cells

The tubule cells show the characteristic changes found in nephrotic glomerular nephritis, i.e. those changes found with heavy proteinuria, intracellular deposits of lipoid, and collections of an eosin-staining material of uncertain origin. Tubular atrophy is also present.

Without the use of special stains it is easy to confuse renal amyloidosis with diabetic nephropathy, and particularly persistent glomerular nephritis.

Clinical Features

Amyloidosis was seen most commonly in sanatoria in patients suffering from chronic tuberculosis of the bones or lungs; it may, however, occur as a complication of chronic sepsis from any cause. Now it is most often seen in rheumatoid arthritis and other diseases in which there is no sepsis, such as myelomatosis. Amyloid also occurs as a familial condition. In one type of familial amyloidosis which is characterised by polyneuropathy, cardiomyopathy and splenomegaly, renal involvement is unusual. In the other the amyloidosis is a complication of Familial Mediterranean Fever. In this type the amyloid deposits in the kidney are the usual cause of death.

Amyloidosis can also occur in patients with no accompanying disease and with no family history of the condition. This form is usually known as primary amyloidosis.

The first indication of renal amyloidosis is proteinuria, and the most common clinical manifestation is the development of a nephrotic syndrome. This may be particularly severe, for the hypoproteinæmia may not only be due to proteinuria but also to a decreased rate of protein synthesis as a consequence of hepatic amyloidosis, and also to an impaired absorption of amino-acids because of amyloid deposits in the mucous membrane of the small bowel.

It is very rare for the presenting symptoms to be those of chronic renal failure; it is characteristic that the blood pressure may often remain normal for a considerable time after the onset.

Occasionally there is a sudden onset of acute renal failure due to renal vein thrombosis. The thrombosis appears to begin in the intrarenal veins and extend medially. A few remarkable cases have been described which have suffered from severe polyuria and polydipsia over many years. In one of these the collecting ducts and vasa recta at post-mortem were found to be surrounded by a thick layer of amyloid material.

Diagnosis

The diagnosis of renal amyloidosis is confirmed by finding the characteristic deposits in a renal biopsy. If it is inappropriate to perform a renal biopsy, a rectal biopsy can be performed. A rectal biopsy will show amyloid deposits in 75 per cent of patients with renal amyloidosis whereas a liver biopsy will only be positive in less than 50 per cent and a gum biopsy in less than 20 per cent

It is important that all renal biopsies which show any deposits of *eosinophilic material should be stained for amyloid Otherwise the* diagnosis will be missed

Treatment

If the disease with which amyloidosis is associated can be controlled particularly if a septic lesion can be excised renal function may improve and the blood pressure will return to normal Otherwise treatment is symptomatic and is that of the nephrotic syndrome (p 132) and chronic renal failure (p 178) Serial renal biopsies from patients with rheumatoid arthritis suggest that once renal amyloidosis is sufficiently severe to cause some impairment in renal function the renal lesions are irreversible Treatment with adrenal steroids may produce a remission of symptoms and proteinuria may cease but the renal lesions remain

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32

SCLERODERMA

THE generalised form of scleroderma not only affects the skin but also the gastro-intestinal tract, the lungs, the heart and the kidney.

Pathology

Renal lesions are uncommon. They consist mainly of a striking thickening of the intralobular arteries and afferent arterioles. One type of thickening consists of intimal proliferation. This may be found in renal biopsies obtained many years before death.

The other lesions develop in the last few weeks of life and rapidly cause the death of the patient from renal failure. The kidneys are swollen and pale, while the cut surface shows a mottled congestion of the cortex which is due to a patchy necrosis. The necrotic lesions are due to occlusion of the proximal portions of many intralobular arteries by a mucoid substance which lies in concentric layers in the intima. The distal parts of some of the intralobular arteries and the afferent glomerular arterioles also show necrosis and fibrinoid changes. Many pathologists find these lesions indistinguishable from those found in malignant hypertension. Isolated polyarteritic lesions and " wire-loop " lesions have also been described, but both changes are inconstant.

Clinical Features

Proteinuria may be present for many years. This is usually associated with some reduction in renal blood flow but little impairment in renal function. Once renal function begins to deteriorate death usually follows within a few weeks. Some patients develop a catastrophic rise in blood pressure. They present with convulsions and rapidly go into coma. Occasionally, the acute deterioration of renal function appears to have been provoked by the use of adrenal steroids, when these have been used to alleviate some of the other symptoms of scleroderma.

Treatment

Treatment is symptomatic.

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33

RADIATION NEPHRITIS

RADIATION nephritis has only been described in patients with malignant tumours of the testicle following irradiation of the periaortic abdominal glands.

Pathology

There is little to see with the naked eye except some fibrous tissue between the kidney and the peritoneum. The capsule, however, is free and the kidney normal in size.

Microscopically the capsule shows considerable fibrous thickening. The glomeruli are smaller than normal and the glomerular loops show replacement with variable quantities of an eosin-staining material. Many of the tubules are atrophic and they are separated by large amounts of intertubular material which in some places includes fibrous tissue.

The larger vessels show no changes, the intralobular arteries and the arterioles may show sclerotic changes (p. 113), and the glomerular capillaries occasionally show necrotic lesions similar to those found in malignant hypertension (p. 113). These necrotic lesions may be present in the kidney even though they are absent from other organs, and the patient has not suffered from malignant hypertension clinically.

Following irradiation of the kidneys in animals the blood pressure rises before any abnormal microscopical changes are evident. It seems probable, therefore, that the vascular lesions that are seen later are due to the hypertension; the cause of the hypertension is unknown.

Acute Radiation Nephritis

Clinical Features

The onset of symptoms attributable to changes in the kidney occurs after a latent period of six to twelve months from the start of radiotherapy. The reason for this interval is not known; it is one of the most interesting points about the disease.

Symptoms develop gradually; they include œdema, dyspnœa, hypertension, headache, nausea and vomiting, lassitude, and nocturia. In most instances the patient has to retire to bed within a month. There is no clear-cut acute nephritic syndrome or nephrotic syndrome.

The condition usually appears as chronic renal failure of rapid onset In all cases there is proteinuria and hypertension, but widespread œdema and cardiac failure seem rather to follow a hypertension of increasing severity than to be an integral part of the initial disturbance Proteinuria is rarely greater than 5 g /day and hypoproteinæmia has not been recorded Some degree of renal failure occurs in all cases and is characteristically associated with severe anæmia

Course

A third to a half of the cases reported in one series died within 4–12 months of the onset of symptoms Death was due to hypertensive cardiac failure, hypertensive fits and renal failure The remainder survived, but continued to have proteinuria, hypertension and some diminution in glomerular filtration rate

Prognosis

A rise in blood urea above 200 mg per 100 ml at some time during the first three months or the development of pleural effusions without generalised œdema are stated to be signs indicative of a poor prognosis

The duration of the latent period, the age of the patient, and the height of the blood pressure in the first five months have no prognostic significance

Treatment

Prophylactic With the greatest care, the dose of X rays needed for secondary seminomas is perilously close to that which can damage the kidney The use of the cobalt bomb should enable the field of irradiation to be so narrowed that renal damage, if it occurs is limited to one kidney and the damaged kidney can then be removed

Curative It is imperative to decide if the renal damage is unilateral or bilateral, for if it is unilateral the blood pressure can be lowered by nephrectomy

Otherwise treatment is symptomatic and includes the control of hypertension, cardiac failure, œdema and renal failure. The necessity for blood transfusions appear to be greater than in other forms of renal failure, their administration is frequently accompanied by generalised reactions

Chronic Radiation Nephritis

Some patients never develop a period of acute renal disorder, but 18 months to several years after irradiation they are found to be suffering from proteinuria, hypertension and some impairment of renal function The cause of this form of radiation nephritis is obscure Some cases have shown no tendency to further deterioration

Malignant Hypertension

Occasionally there is a sudden onset of malignant hypertension. It may or may not be accompanied by renal failure. Death occurs within a few weeks.

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34

CONGENITAL, MACROSCOPIC, STRUCTURAL LESIONS OF THE KIDNEY

THE term " macroscopic ' is inserted in the title of this section in order to exclude the congenital microscopic structural lesions of the tubules which are associated with innate functional defects (p 209)

The following malformations will be discussed

Renal agenesis
  (*a*) Bilateral
  (*b*) Unilateral
Renal hypoplasia
  (*a*) Bilateral hypoplasia
  (*b*) Unilateral dwarfed kidney
Renal ectopia
Anomalies due to fusion
  (*a*) Horseshoe kidneys
  (*b*) Unilateral fused kidney crossed renal ectopia
Duplication of pelvis and ureter
Cystic disease of the kidneys
  (*a*) Polycystic kidneys
  (*b*) Solitary cysts
  (*c*) Cystic disease of the medulla
  (*d*) Sponge kidney

RENAL AGENESIS

Bilateral Agenesis *is not compatible* with life, though occasionally the infant may live for two to three days Not only are the kidneys absent but the ureters are often rudimentary Other congenital abnormalities, such as spina bifida, are always present. Bilateral agenesis can sometimes be suspected during pregnancy for it is often associated with oligohydramnios

Clinical Note Unilateral congenital renal structural abnormalities are often associated with a homolateral illshaped external ear There may only be some prominence shortening or absence of the lobe or there may be severe distortion This can sometimes be a useful clue in a child with a fever of unknown origin

Unilateral Agenesis (Fig. 34.1) is more common than bilateral agenesis and may not be discovered until autopsy for some other disease. It occurs equally in both sexes and is more frequent on the left side. The remaining kidney hypertrophies and often weighs as much as a normal pair of kidneys.

Other congenital abnormalities may be found; in children gross abnormalities, such as meningocœle are not infrequent; in adults they are found less often and occur mainly in the genital tract, for instance, there may be a bicornuate or a double uterus.

RENAL HYPOPLASIA

Bilateral Hypoplasia usually causes death shortly after birth. Very rarely it may produce a state of chronic renal failure after two to three years of life.

Unilateral Hypoplasia has to be differentiated from acquired unilateral disease, for chronic urinary obstruction or infection may also result in a remarkably small kidney. As this differentiation is sometimes very difficult, the term *unilateral dwarfed kidney* is used to include those kidneys which are unequivocally hypoplastic, and those in which hypoplasia is the most likely diagnosis.

By combining the incidence of unilateral agenesis and hypoplasia, Bell has calculated from his autopsy records that in persons over one year of age the chance of there being only one kidney capable of sustaining life is about 1/200.

RENAL ECTOPIA

Ectopic kidneys are usually situated either in the iliac fossæ, including the brim of the pelvis, or in the pelvic cavity (Fig. 34.1). They occur equally in the two sexes, and are rather more common on the left side. In the iliac fossæ they show no major structural alteration, but when they are in the pelvis they may be seriously distorted. Frequently the kidney is hypoplastic; the renal pelvis is usually directed forward and the ureter is often dilated and tortuous. The renal artery arises from the nearest part of the aorta or the common iliac artery.

Ectopic kidneys may function normally, but they are liable to hydronephrosis and pyelonephritis.

Clinical Features

Lower abdominal pain or discomfort, dysuria, frequency and hæmaturia are the presenting symptoms; or proteinuria may be found during a routine examination. Occasionally an ectopic kidney may first be diagnosed during pregnancy and may be confused with a tumour of pelvic abscess; an intravenous pyelogram allows the right diagnosis to be made only if the kidney can excrete the radio opaque material; at other times a retrograde pyelogram or laparotomy is necessary.

Often there are other congenital abnormalities.

Movable Kidney

The mobility of the kidney may be greater than normal but it is *extremely doubtful if excess mobility is ever the* cause of symptoms, or makes the kidney more liable to infection or other disorders At one time, however, numerous operations were performed to secure errant kidneys into more conventional sites. Most of the operations *were performed in* that notorious group of middle-aged women who complain of vague abdominal pains.

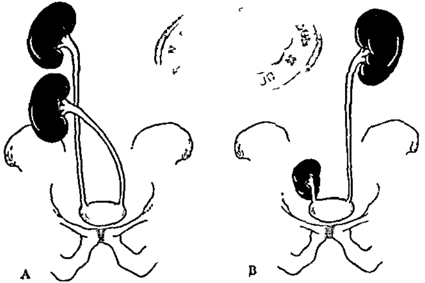

Fig 34 1 Renal ectopia (*a*) Both kidneys on the same side, and (*b*) Unilateral pelvic kidney

ANOMALIES DUE TO FUSION

Horseshoe Kidney

This malformation consists in the fusion of two poles of the kidneys, usually the lower poles, across the midline. The two pelves are always separate and point in a forward direction, the two ureters travelling anteriorly over the surface of the lower poles (Fig. 34.2).

Horseshoe kidneys occur more frequently in males; and in persons over one year of age Bell found the incidence to be 1:400. There is no conclusive evidence that this abnormality is associated with a greater frequency of renal diseases than are normal kidneys.

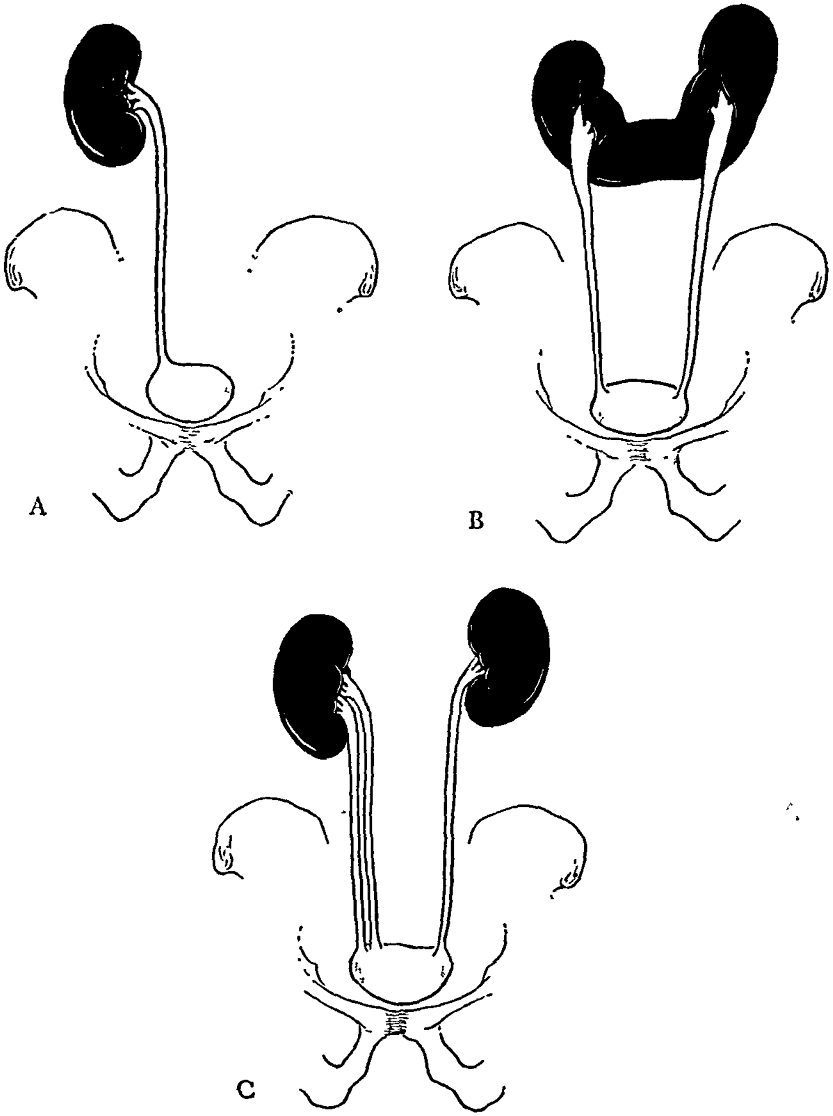

Fig. 34.2. (*a*) Unilateral agenesis, (*b*) Horseshoe kidney, (*c*) Double ureter.

Unilateral Fused Kidney

Very rarely both kidneys may be fused together on one side of the body Both ureters enter the bladder in their normal sites, so that one ureter has to travel across the midline and is thus more liable to cause hydronephrosis and infection

DUPLICATION OF PELVIS AND URETER

This anomaly is more common in women and is found most frequently on the left side, it is not unusual for it to be bilateral when it is more extensive on one side than the other The two ureters from one kidney may be completely separate in their course to the bladder, so that there are two ureteric orifices to one side of the midline (Fig 34 2) At other times the two ureters fuse together either in the bladder wall or somewhere between the pelvis and the bladder Occasionally one ureter may enter the vagina, the urethra, the seminal vesicles or the vas deferens This is often the ureter from the upper part of the kidney while the ureter from the lower part enters the bladder in the normal place

Duplication of the pelves and ureters is often associated with pain hydronephrosis and recurrent urinary infection

CYSTIC DISEASE OF THE KIDNEYS

A malformation which may be unilateral or bilateral Bilateral cystic disease of the kidneys is far more frequent and important clinically

Bilateral Polycystic Kidneys

This is a hereditary condition which declares itself clinically either in infancy (the neonatal form), or in middle age (the adult form), in childhood and up to the age of 20 the incidence falls off to negligible proportions The reason for this remarkable division of incidence is not known It is possible that the two forms of the disease, though they appear almost indistinguishable structurally, may stem from different ætiologies In favour of this theory is the fact that the adult form appears to be inherited as an autosomal dominant in families in which there are a number of other cases, whereas the neonatal form appears to be due to an autosomal recessive There are no records of adult and neonatal cases occurring in the same family

Both forms occur equally between the two sexes

Pathology

Both kidneys tend to be considerably enlarged, though the degree of enlargement may be unequal (Fig. 34.3). Each consists of a compact mass of cysts. On section the cysts are seen to be scattered equally in the cortex and medulla, and usually there does not seem to be any intact parenchyma. On rare occasions the cysts may be limited to one pole. In the neonatal disease all the cysts tend to be of a similar size, whereas in adults they vary considerably and some may be exceedingly large.

The cysts are filled with a watery fluid which may be clear, blood-stained from recent hæmorrhage, or brown from an old hæmorrhage; some may be filled with pus. They are lined by a single layer of epithelium and occasionally a normal glomerular tuft may be found invaginated into the cavity of a cyst, when the cyst is then considered to be the distended capsular space of that glomerulus. Cysts do not often communicate with the pelvis of the kidney.

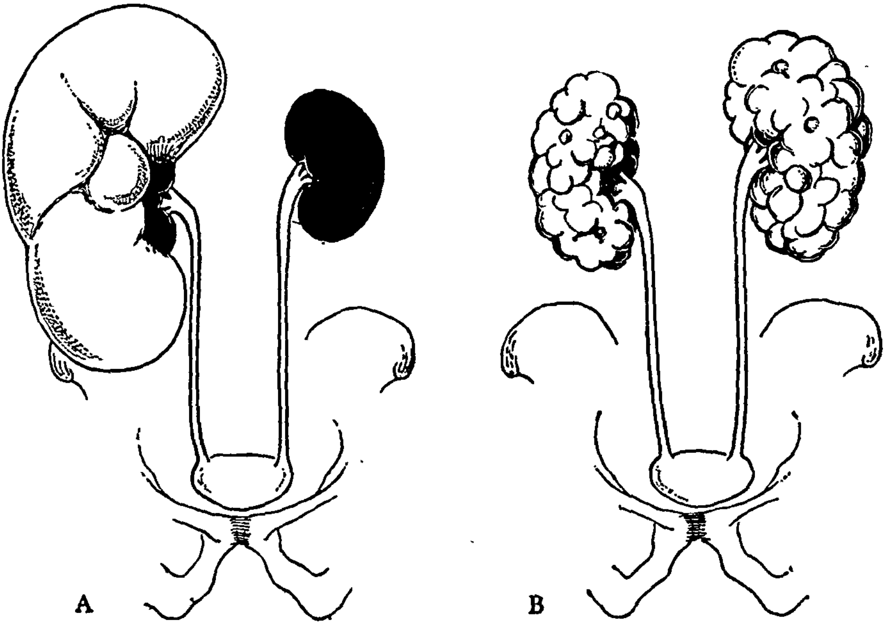

FIG. 34.3. (*a*) Solitary cyst, (*b*) Polycystic kidneys.

It can be demonstrated that the contents of some cysts are in a continuous flux with the circulation, e.g. inulin placed in the cysts will appear in the blood and vice versa. It has been suggested therefore that the cysts have some renal " functional " capacity, however trivial. Unless the cysts are joined to the pelvis, however, this is of no consequence whatever its extent.

Liver cysts are found in one third of patients with polycystic kidneys and there is also a significant association with aneurysms of the cerebral arteries

Pathogenesis

There are many theories but " nothing certain is known " (Dalgaard, 1957).

Clinical Features

Neonatal form Usually neonatal bilateral cystic kidneys cause stillbirth, and sometimes their size may cause serious difficulties during delivery The infant may live for a few months or one to two years, only to succumb to chronic renal failure

Adult form The onset of the presenting symptoms usually occurs when the patient is about 40 years old, but the age of onset may range from 8 years to 77 years These may be entirely renal with hæmaturia, clot colic, or acute pyelonephritis, or they may be more generalised, when they are due to renal failure or hypertension Sometimes the

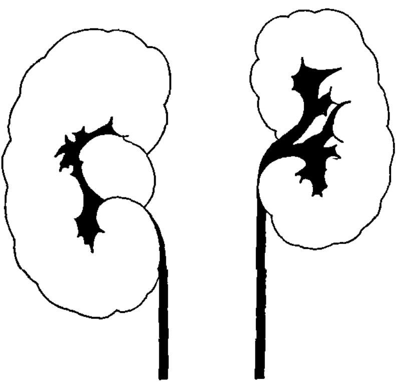

FIG 34 4 Polycystic kidneys. An intravenous pyelogram illustrating the distortion of the pelvis and calyces by the cysts patient complains of abdominal distension, or pain following some relatively minor trauma. Proteinuria is always present and may be the first abnormality to draw attention to the renal disease.

Hypertension develops in only about 75 per cent of cases and is rarely malignant. As renal failure develops the usual fall in hæmoglobin tends to be less pronounced than in other forms of renal disease. In some patients there is no significant fall in hæmoglobin.

By the time the patient begins to complain of symptoms the kidneys are usually easily palpable and have a characteristic " knobbly " feel. The diagnosis is confirmed by an intravenous pyelogram which shows the pelvis to be elongated with the calyces stretched out, and their peripheral ends shaped into crescents of varying sizes (Fig. 34.4). Early disease showing only unilateral abnormalities may be difficult to differentiate from solitary cysts or a tumour.

Prognosis

The rate of renal impairment and the pattern of events varies enormously from patient to patient, but certain families show a tendency towards a recurring pattern.

Death is due either to chronic renal failure from compression of the renal parenchyma by the enlarging cysts, and chronic renal infection; or from hypertensive cardiac failure, and cerebrovascular accidents. Hypertensive cardiac failure is the most common immediate cause of death.

The average age of death is about 50 years, i.e. the average duration of the disease once it has become manifest is 5 to 10 years. There are wide variations around these means, however. If renal infections are promptly treated some patients live many years without appearing to deteriorate.

Treatment

If the disease is almost confined to one kidney which is subject to recurrent infections and is functionally useless it may be wise to remove it, after first establishing that the function of the other kidney is adequate.

When the disease is bilateral the only measure which may cause any improvement is the evacuation of some of the larger cysts in order to relieve the pressure upon the residual parenchyma. The functional results of such operations, however, have not often been investigated; attention has been paid rather to the improvement in appearance of the intravenous pyelogram, and the continued survival of the patient. Until now there has not been a convincing demonstration that the operation will in fact prolong life; some authorities categorically deny that renal function is improved Nevertheless, there is general agreement that the operation is sometimes most useful in the relief of recurrent pain and hæmaturia and that occasionally there has been relief of hypertension It is considered that the operation should only be performed on one side at a time, for there is often a relatively severe transient post operative deterioration in renal function

Otherwise, treatment is symptomatic and is that of renal failure, renal infection, hypertension and cardiac failure

If the patient suffers from migraine or has a cerebrovascular accident special attention should be given to the possibility of cerebral aneurysm If renal function is good prompt treatment of the aneurysm may extend life

Solitary Renal Cysts

Small cysts are frequently found during routine autopsies their size usually precludes them from having caused any ill effects

Large "solitary" cysts are rarely single but occur in clusters of two or three (Fig 34 3) They are more common on the right side and more often seen in women They may be situated in either pole or in the middle of the kidney nearly always they spring from the parenchyma, but occasionally they may be entirely sub or extracapsular The parenchyma near the cyst is always considerably compressed They only rarely have a connection with the pelvis The contents of the cysts contain 500–1 000 ml of yellow or blood stained fluid and sometimes considerably more The walls of the cysts are composed of thin fibrous tissue in which a few atrophic tubules may be seen

Clinical Features of Large Cysts

The main complaint is of intermittent attacks of abdominal pain interspersed by long remissions The attacks tend to become more frequent as the years go by and the total duration of the history may be 20–30 years The pain may be associated with fever dysuria and occasionally with hæmaturia Painless hæmaturia is sometimes the first symptom

Cysts in the upper poles are particularly difficult to palpate and when on the right side may cause symptoms resembling cholecystitis Lower pole cysts cause gastric and intestinal symptoms, with nausea or diarrhœa, they are also liable to obstruct the ureter and cause renal infections

The diagnosis should be evident from an intravenous pyelogram, which may show compression of the calyces and elongation of the pelvis Often the appearances are difficult to differentiate from those of a tumour, and sometimes the radiological appearances are normal

Treatment

This is surgical. If possible, a heminephrectomy is performed, otherwise a total nephrectomy is necessary.

Cystic Disease of the Renal Medulla

This condition destroys the patient either in adolescence or early adult life. The patient presents with severe thirst and polyuria and is found to have renal failure with a pronounced urinary sodium leak. The intravenous pyelographic changes have not been described. The kidneys at post-mortem show multiple cysts in the medulla and sometimes a few in the cortex together with cortical atrophy.

Sponge Kidney

This is a radiological diagnosis of a relatively benign condition which is not usually diagnosed until adulthood. The I.V.P. may be performed because of a urinary infection or hæmaturia. The preliminary picture may show areas of calcification in the medulla. After the dye has been injected the I.V.P. shows multiple discrete opacifications in the pyramidal areas before the pelvis and calyces become opacified. These medullary opacities are grouped at the tips of the calyces and appear to branch away from them like a bouquet of flowers. It is characteristic that a retrograde pyelogram shows a completely different picture, for most of the cysts have such small connections into the calyces that they are not filled from below. There are very few descriptions of the structural changes and these are mainly from surgical specimens. They show collections of small cysts in the pyramids and medulla but the cortex is normal.

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Appendix 1

DIETS

HIGH PROTEIN, LOW SODIUM DIET

Protein Content 180–190 g.
Sodium Content 30–40 mEq.

Meal	oz.	g.	*Food*	*Protein* g.	*Sodium* mEq.
Breakfast	5	142	Porridge	2	0·3
	2	57	Unsalted bread	4	0·2
	½	14	Unsalted butter or margarine	—	0·2
	4	114	2 eggs, cooked in any way	14	6·6
			Milk from daily allowance for porridge and tea or coffee		
			Sugar as desired	—	—
	½	14	Marmalade, honey or jam	—	0·2
Dinner	5	142	Lean meat, cooked weight	35	4·1
	4	114	Potatoes, boiled, roasted or fried	2	0·2
			Vegetable or salad, average helping	0·5	0·5
			Stewed or tinned fruit, average helping	0·5	0·5
			Pudding using high protein Edosol milk from daily allowance		
Tea	2	57	Unsalted bread	4	0·2
	½	14	Unsalted butter or margarine	—	0·2
	2	57	Lean meat as sandwich filling	14	2·2
			Tea with milk from daily allowance		
			Sugar as desired		
	1	28	Cake made from low sodium ingredients (see general instructions)	2	0·4
Supper	6	170	Fried fish (cooked weight)	35	12·0
	4	114	Potatoes, boiled, roasted or fried	2	0·2
			Vegetable or salad, average helping	0·5	0·5
			Fruit, average helping	0·5	0·5
			Pudding using high protein Edosol milk from daily allowance		
Daily	4	114	Ordinary milk for tea	4	2·5
	25	710	Edosol milk reconstituted +	25	1·1
	1½	43	Casilan for drinks and puddings	39	1·8
				184	34·4

All foods cooked without salt.

In this diet, if ordinary milk is substituted for Edosol the sodium will rise by 14·6 mEq., and if ordinary bread and butter are substituted for the low sodium varieties the sodium will rise by 22 mEq.

General Instructions

Edosol is a low sodium synthetic milk powder made by Trufood reconstituted according to the directions on the tin Casilan is a calcium caseinate, a 90 per cent soluble protein made by Glaxo.

The mixture of Edosol and Casilan can be used in place of ordinary milk to make cereal milk puddings, custard, egg custard, milk jelly, as well as in drinks flavoured with milk shake syrups, coffee and malted drinks It is not suitable for use in tea

To make a low sodium diet interesting, use pepper, mustard, vinegar, lemon juice, home made unsalted chutney and pickles Herbs such as bay leaves, thyme and sage, and spices such as curry, cayenne pepper, paprika, cloves and nutmeg. To improve the flavour fry potatoes and other vegetables, toast the bread and use garlic and onions liberally.

Foods low in sodium not mentioned previously

Most frozen vegetables.

Lard, dripping, olive oil, dairy cream, Matzo, Rakusen's unsalted crackers shredded and puffed wheats, unsalted yeast extract made by Marmite

Low sodium canned peas and baked beans in tomato sauce are obtainable through Boots.

Recipe for low sodium baking powder, for use with plain flour

Starch . . .	28 g
Potassium bicarbonate .	40 g
Tartaric acid . .	8 g
Potassium bitartrate . .	56 g

This recipe can be made up by any chemist It should be used like ordinary baking powder.

Avoid

All bread if not specially made without salt
Crispbreads such as Ryvita, cream crackers
Ordinary cakes and biscuits
Self raising flour
Cornflakes.
Smoked, tinned and shell fish.
Shop-prepared meats and pies, tinned meat, sausages, bacon, ham, meat and fish pastes
Cheese, except home-made unsalted
Salted butter and margarine.
Tinned vegetables, tinned tomato juice
Tinned soups, shop pickles, sauces, salad cream.
Meat and yeast extracts. Golden syrup Rennet.
Chocolate and toffees above 1 oz per day
Sodium bicarbonate. "Health salts" Liquorice.
Beer, over ½ pint daily.

General instructions for Low Protein diets

To obtain a positive nitrogen balance at least 3,000 calories should be taken per day. The calorie content of the 20 g. and 40 g. protein diets are 1,500 and 2,000 calories respectively. The additional calories are derived from the following foods:—

Hycal, glucose, fruit squash, fruit juice, lemonade, boiled sweets, peppermints, jam, honey, marmalade, unsalted butter, lard, cooking oils, wheat starch, protein-free pastas and protein-free bread and biscuits.

In the Low Protein diets with sodium restriction, all foods should be cooked without salt. In addition salty foods such as bacon, ham, sausages, tinned meat, tinned fish, smoked fish, tinned vegetables, pickles, etc. should be avoided.

Hycal, produced by Beecham Laboratories, is a high calorie electrolyte free drink. One bottle contains 415 calories. Protein-free flour, bread and biscuits, either salted or unsalted, are available from Welfare Foods (Stockport) Ltd. and may be prescribed on form E.C.10. Low-protein pasta is produced by Carlo-Erba, Milan.

LOW PROTEIN, LOW SODIUM DIET

Protein Content 40 g., Sodium Content 28 mEq.

Meal	*oz.*	*g.*	*Food*	*Protein* *g.*	*Sodium* *mEq.*
Breakfast	1	28	Milk	0·9	0·6
	2	56	Egg	6·8	3·3
	1	28	Bread, ordinary	2·4	6·8
	½	14	Butter	—	1·5
	4	112	Fruit and Sugar	0·4	0·1
	½	14	Marmalade, honey, syrup	—	—
Dinner	1½	12	Meat, cooked weight	10·5	1·2
	3½	98	Green vegetables	1·2	0·3
	3½	98	Root vegetables	0·7	1·0
	4	112	Potato	1·6	0·2
	4	112	Fruit and sugar	0·4	0·1
	1	28	Double cream	0·4	0·3
Tea	1	28	Milk	0·9	0·6
	1	28	Bread, ordinary	2·4	6·8
	½	14	Butter	—	1·5
	½	14	Jam, honey or syrup	—	—
	4	112	Fruit	0·4	0·1
Supper	1	28	Meat, poultry, offal or fish	7·0	1·2
	3½	98	Green vegetables or salad	1·2	0·4
	3	84	Potato	1·2	0·15
	½	14	Butter	—	1·5
	4	112	Fruit and sugar	0·4	0·1
	1	28	Double cream	0·4	0·3
Daily	3½	98	Sugar	—	—
				39·2	28·05

VERY LOW PROTEIN, NORMAL SODIUM DIET

Protein Content 20 g.

Meal	*oz.*	*g*	*Food*	*Protein g*
Breakfast	4·0	112	Fruit average helping raw or stewed with sugar	0·5
	1	28	Bread, plain or toasted—1 slice from a cut loaf	2·2
			Butter or margarine	
			Marmalade, honey or jam	
			Tea with sugar and lemon or coffee with sugar	
Dinner	1	28	Meat or cheese or	
	1½	43	Fish or	
	2	56	Egg	7
	1	28	Bread or	
	5	140	Potato—1 medium sized, fried if desired	2
			Vegetables or salad, average helping, not *including peas or butter beans*	*0·5*
			Fruit, average helping, raw or cooked with sugar	0·5
Tea	1	28	Bread	2·2
			Bread or margarine	
			Jam or honey	
			Tea with sugar and lemon	
Supper or High Tea	2	56	As Dinner (omitting meat or alternative)	3·0
Daily			Milk—4-tablespoons	1·8
				19·7

Alternatives

1	28	Breakfast cereal	2
1	28	*Biscuits, most kinds*	2
3	84	Boiled rice (or 1 oz (28 g) of raw rice)	2
1	28	Cake, average	2
1	28	Pastry, short	1
1	28	Pastry, flaky	1·5
1	28	Custard, made from powder	1
1	28	Jelly, prepared	0·5
1	28	Dairy cream	0·5
1	28	Shelled peanuts	8
1	28	Brazil or walnuts	4
1	28	Butter beans, haricot beans, tinned peas	2
1	28	Milk chocolate	2
1	28	Plain chocolate	1·5

VERY LOW PROTEIN, LOW SODIUM DIET

Protein Content 20 g., Sodium Content 20 mEq.

Meal	*oz.*	*g.*	*Food*	*Protein g.*	*Sodium mEq*
Breakfast	4	112	Grapefruit segments	0·8	0·1
	1	28	Bread, plain or toasted, ordinary	2·4	6·8
	½	14	Butter	—	1·5
			Marmalade	—	—
			Tea or coffee	—	—
	1	28	Milk	0·9	0·6
Dinner	1	28	Meat or	7·0	0·8
	1½	43	Fish or	7·0	3·0
	1	56	Egg	7·0	3·3
	2	56	Potato	0·8	0·1
	3½	98	Root vegetable	0·7	1·0
	3½	98	Green vegetable	1·2	0·3
	4	112	Fruit	0·4	0·1
	1	28	Cream	0·4	0·3
Tea	½	14	Bread, ordinary	1·2	3·4
	½	14	Butter, ordinary	—	1·5
			Jam or salad		
			Tea or coffee with 1 oz. milk	0·9	0·6
Supper	2	56	Potato	0·8	0·1
	3½	98	Root vegetable } or salad	0·7	1·0
	3½	98	Green vegetable }	1·2	0·4
	4	112	Fruit	0·4	0·1
Daily	1	28	Cream	—	—
	3½	98	Sugar	—	—
				20·2	19·0
			Alternatives		
	1	28	Biscuits, salt free	2	—
	3	84	Boiled rice 1 oz. or (28 g.) raw rice	2	0·03
	1	28	Cake, salt free	2	—
	1	28	Butter beans, haricot beans, tinned peas (Dietade)	2	0·2
	1	28	Jelly, prepared	0·5	—
	1	28	Cream, double	0·4	0·1

PROTEIN, SODIUM AND POTASSIUM CONTENT OF CERTAIN FOODS

Food	*Protein g /100 g*	*Sodium mEq /100 g.*	*Potassium mEq /100 g*
Cheese (Cheddar)	24·9	26·6	3·0
Cow's milk	3·3	2·2	4·1
Cream (double)	1·5	1·1	2·0
Edosol milk (reconstituted)	3·5	0·1	18·2
Complan	31·0	17·4	28·2
Casilan	90·0	4·3	0·1 (less than)
Ice cream	4·1	3·4	4·3
Horlicks	14·4	30·0	29·0
Egg	11·9	5·9	3·5
Beef (steak with fat, grilled)	25·2	2·9	9·4
Beef (stewed lean only)	30·8	1·7	3·9
Mutton (leg with fat, roasted)	25·0	3·1	8·9
Mutton (chop, fried, lean only)	22·8	5·0	9·0
Chicken (boiled)	26·2	4·3	9·8
Ham (boiled)	23·1	91·3	11·6
Liver (calf, fried)	29·0	5·3	10·5
Tongue (ox, pickled)	19·1	61·0	3·9
Veal (cutlet, fried)	30·4	4·6	10·8
Sausage (pork, fried)	11·5	43·0	5·3
Cod (steamed)	18·0	4·3	9·2
Cod (fried in batter)	20·7	7·0	8·8
Cod (grilled)	27·0	4·8	10·5
Herring (fried)	21·8	4·4	10·6
Oysters	10·2	22·0	6·6
Plaice (steamed)	18·1	5·2	7·1
Plaice (fried in batter)	18·0	5·4	5·6
Porridge (cooked)	1·4	0·2	1·8
Cornflakes	6·6	45·6	2·9
Energen flakes	36·8	0·3	3·9
Bread (white)	8·1	17·1	1·8
Ryvita	6·8	26·7	12·0
Cream crackers	8·5	19·0	3·3
Puffed wheat	13·9	0·25	11·5
Bread (unsalted, white)	8·1	0·3	1·8
Energen rolls (per roll)	2·0	0·1	0·1
Flour	8·6	0·01	4·5
Spaghetti	9·9	0·2	4·01
Rice (boiled)	2·1	0·1	1·0
Butter or margarine	—	9·6–14·0	0·1—1·0
Butter or margarine (unsalted)	—	0·1	0·1–1·0

Foods High in Potassium and Low in Protein

	Food	*Potassium* mEq./100 g.
Cereals	All Bran	24·5
	Malt bread	9·5
	Ryvita	12·0
Fruit and nuts	Apricots—dried, stewed	20·0
	Apricots—tinned in syrup	6·6
	Bananas	8·9
	Dates	19·3
	Figs—dried, stewed	14·8
	Grapes—black	8·1
	Prunes—dried, stewed	8·5
	Chestnuts—shelled	12·7
Vegetables	Beetroot, boiled	9·0
	Mushrooms, fried	14·5
	Potatoes, old and new boiled	8·4
	Potatoes, baked in skin	17·4
	Potatoes, roasted	19·1
	Potatoes, chips	26·2
	Spinach, boiled	12·6
	Tomatoes, fried	8·6
		mEq per teaspoon
Drinks	Bovril	5·5
	Marmite	4·4

Food values have been obtained from McCance and Widdowson's tables*; in some instances average figures have been used.

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* McCance, R. A., and Widdowson, E. M. (1946). The Chemical Composition of Food. *Med. Res. Coun. Spec. Rep. Ser.*, No. 235.

Appendix 2

SOME NORMAL VALUES

RENAL FUNCTIONAL CAPACITY

Some Normal Values for Young Subjects, 1·73 sq. m. Surface Area

Renal plasma flow	612 ± 68 ml./min
Renal blood flow	Approximately 1,200 ml./min
Glomerular filtration rate	
1. Inulin clearance	112 ± 15 ml./min Adult males by age groups* 20–29 yrs 123 ± 16 ml./min 50–59 yrs 99 ± 15 ml./min 80–89 yrs 65 ± 20 ml./min
2. Creatinine clearance	Approximately the same as inulin
Urea clearance (at urine flows greater than 2 ml./min.)	75 ml./min
Maximal Tubular Capacity (Tm)	
1. To reabsorb glucose	323 ± 64 mg./min.
2. To secrete PAH	68 ± 11 mg./min
Ability to concentrate (*Fluid deprivation*)	*800 to 1,200 m. osmole/l* (i.e. S.G. 1·022 to 1·032)
Ability to dilute	40 to 80 m. osmole/l (i.e. *S.G. 1·002*)
Ability to excrete a water load of 1 litre	800 ml. excreted in next 4 hours.

*Shock, N. W. (1946). "Kidney function tests in aged males." *Geriatrics*, 1, 232

DAILY URINARY EXCRETIONS

Twenty-four-hour output, on a mixed diet. These figures are given only as a guide

AMMONIA	30 to 60 mEq.
CALCIUM	80 to 400 mg.
COPROPORPHYRIN, total	14 to 100 µg.
CHLORIDE	80 to 200 mEq
CREATINE:	
Children	up to 150 mg
Women	small amounts
Men	nil
CREATININE	0·8 to 1·8 g.
DIASTASE	8,000 to 30,000 units
GLUCOSE	16 to 132 mg.
POTASSIUM	80 to 200 mEq.
*p*H	4·8 to 7·4
SODIUM	80 to 200 mEq.
TITRATABLE ACID (Hydrogen ion)	20 to 30 mEq.
UREA	16 to 35 g.
URIC ACID	0·1 to 2·0 g.
UROBILINOGEN	Less than 2 mg.
VOLUME	1,000 to 2,000 ml.

PLASMA CONTENTS

		Useful average
ALBUMIN	4·0 to 5·7 g./100 ml.	4·8 g./100 ml.
ALBUMIN/GLOBULIN RATIO	1·2/1 to 4/1	2/1
BICARBONATE (see CARBON DIOXIDE)		
BILIRUBIN (total)	Less than 0·8 mg./100 ml.	
CALCIUM	Total . . 8·5 to 10·5 mg./100 ml.	9·5 mg./100 ml.
	Diffusible . 3·6 to 5·6 mg./100 ml.	
	Non-diffusible 2·8 to 6·1 mg./100 ml.	
CARBON DIOXIDE	25 to 31 mEq./l.	27 mEq./l.
CHLORIDE	99 to 108 mEq./l.	103 mEq./l.
CHOLESTEROL	Total, 120 to 240 mg.100 ml.	200 mg./100 ml.
	Ester, 60 to 80% of total	70% of total
CREATINE	0·2 to 0·6 mg./100 ml.	0·4 mg./100 ml.
CREATININE	0·8 to 1·4 mg./100 ml.	1 mg./100 ml.
DIASTASE	90 to 160 units/100 ml.	
FIBRIN(OGEN)	200 to 400 mg./100 ml.	300 mg./100 ml.
GLOBULIN	1·5 to 3·0 g./100 ml.	2·4 g./100 ml.
GLUCOSE: *Capillary*	Fasting or noon, 80 to 120 mg./100 ml.	100 mg./100 ml.
Venous	About 10 mg./100 ml. lower	
OSMOLALITY	275–285 m. osmole/kg/H_2O	280 m. osmole/kg/H_2O
*p*H	7·37 to 7·4	7·40
PHOSPHATASE: *Alkaline*	King-Armstrong, 3 to 13 units/100 ml.	
	Bodansky, 1·5 to 4·0 units/100 ml.	
Acid	King-Armstrong-total 1 to 5 units/100 ml.	
	King-Armstrong-formaldehyde stable, 0 to 4 units/100 ml.	
PHOSPHORUS (inorganic)	Adults, 2·4 to 4·5 mg./100 ml.	4·0 mg./100 ml.
	Children, 4·0 to 6·5 mg./100 ml.	
POTASSIUM	4·0 to 5·5 mEq./l.	5 mEq./l.
SODIUM	137 to 148 mEq./l.	142 mEq./l.
SULPHATE	0·5 to 1 mEq./l.	
UREA	15 to 35 mg./100 ml. (adults)	25 mg./100 ml.
	10 to 25 mg./100 ml. (pregnancy)	
URIC ACID	2 to 6 mg./100 ml. in women	5 mg./100 ml.
	2 to 7 mg./100 ml. in men	

APPROXIMATE COMPOSITION OF VARIOUS BODY FLUIDS

FLUID	HCO_3 mEq./l.	Cl mEq./l.	P *mM./l.	Na mEq./l.	K mEq./l.	Protein g./l.	Water g./l.
Serum	25	100	2	142	4·3	70	940
Interstitial fluid	28	111	—	145	3·3	traces	993
Spinal fluid	21	125	—	147	2·8	0·3	993
Gastric juice	—	145	—	50	12·0	mucus	993
Bile	38	108	—	150	5·0	mucus	990
Pancreatic juice	110	40	—	140	5·0	mucus	993
Jejunal juice	30	110	—	138	5·0	mucus	993
Sweat†	—	40	—	42	—	—	993
Intracellular fluid:		mEq./kg.	mM./kg.	mEq./kg	mEq./kg.	g./kg.	
Skeletal muscle amounts per kg. of intracellular water	—	3	107	7	155	306	

*mM, or millimole, is the molecular weight in milligrams.

†The composition of sweat may vary considerably.

Body Contents of Sodium and Potassium Red Cell Mass and Fluid Volumes

	Man *70 Kg*	*Woman* *57 Kg*
Total exchangeable Sodium	2 950 mEq	2 250 mEq
Total exchangeable Potassium	3 200 mEq	2 300 mEq
Plasma Volume	2 83 l	2 40 l
Red cell Mass	2 1 l	1 8 l
Extra-cellular fluid	14 l	11 l
Intra cellular fluid	25 l	20 l
Total body water	39 l	31 l

Equivalent and Molecular Weights

Equivalent Weights

N	14	Mg	12
K	39	P	16 (variable)
Ca	20	Cl	35 5
Na	23	O	8

Molecular Weights

Na Citrate ($2H_2O$)	294 0
Na Cl	58 5
Na Lactate	112 0
Na HCO_3	84 0
Na_2 HPO_4 ($12H_2O$)	358 2
Na H_2PO_4 (H_2O)	156 0
K HCO_3	100 1
K Cl	74 6
K_3 Citrate (H_2O)	324 4
K Acetate	98 1
K_2 HPO_4	174 2
NH_4 Cl	53 5
Ca gluconate (H_2O)	448 4
Ca Cl_2	111 0
Ca Lactate ($5H_2O$)	308 3
Mannitol	180 0
Glucose	180 2

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